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JMHSJ
Jambura Medical and Health Science Journal

PENGANTAR EDITOR

Salam sehat,

Alhamdulillah edisi kedua Jambura Medical and Health Science Journal kembali dapat diterbitkan. Sebagaimana pada edisi sebelumnya, maka jurnal terbitan Fakultas Kedokteran UNG pada edisi kali ini menampilkan 2 Review article yang ditulis oleh sejawat Desi Dwi Rosalia Suparman dari FK UNIBOS dan Naning Suleman dari FK UNG/RSAS. Selanjutnya ada 2 *Case Report* yang ditulis oleh sejawat Ilzy Jum Ahmad *et al.* dari FK UNHAS/RSWS dan Winansih Gubali dan Annisa DS dari FK UNG/RSAS. Terakhir ada 1 *Original Article* yg ditulis oleh mahasiswa kita, Alian Ridho *et al.* dari FK UNG. Hal ini menunjukkan JMHSJ sudah diminati oleh para peneliti dari luar institusi Universitas Negeri Gorontalo

Topik yang diangkat pun bervariasi mulai dari abses otak, kanker payudara ,efusi perikardial, retina sampai terkait pembelajaran praktikum histologi. Semoga kedepan akan lebih banyak tulisan dari berbagai disiplin ilmu kedokteran yang diangkat dalam JMHSJ. Selamat membaca.

Gorontalo, 1 September 2022

Dr.dr. Muhammad Isman Jusuf,Sp.N

Chief Editor

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REVIEW ARTICLE **Open Access**

Active Immunotherapy of Breast Cancer Treatment

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ABSTRACT

Background: Immunotherapy as a specific molecular targeted therapy could modulate immune response through cytotoxic CD8+ pathway so that generate anti-tumor activity on breast cancer. HER2/Neu is the one of tumor associated antigen which extensively studied to reduce cancer progression. CTLA-4 has important role in immune checkpoint blockade that it is used for studying breast cancer either in early or advanced level
Content: In this review, we discussed principle of immunotherapy in tumor microenvironment and some kinds of active immunotherapies, which included cancer vaccination and immune checkpoint blockade. Majority of those immunotherapies are ongoing clinical trial.
Conclusion: Active immunotherapy may become a promising new field in breast cancer therapies in a future and will ultimately change the current status of breast cancer therapies.

Keywords: CTLA-4; HER2/Neu; immunotherapy; immune checkpoint; MUC-1; PD-1

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Introduction

Breast cancer is a carcinoma originating from breast tissue that is often found in women, but is sometimes found in men as well. Data from The International Agency for Research on Cancer (IARC) 2020 states that breast cancer, together with lung and colorectal cancer, are the three cancers with the highest incidence and are among the top five causes of death.[1] In Indonesia alone, GLOBOCAN 2020 data shows breast cancer is the first cancer with new case findings (16.6%) in both men and women.[2] In 2018, The Center of Data and Information of Health Ministry of Indonesia (Infodatin) noted that prevalence of cancer among women was 2,85.[3]

The exact cause of breast cancer is not fully known. However, like cancer in general, breast cancer occurs due to various factors that are not fully related, such as genetic factors in the family, endogenous and exogenous hormonal exposure, environment, and sociobiology associated with an unhealthy lifestyle.[4] Breast cancer therapy has continued to evolve in recent decades and involves a variety of strategies including surgery, chemotherapy, ablation, radiotherapy, hormonal therapy, and interventions with molecules, antibodies, or antigens/adjuvants to inhibit cell growth, proliferation, survival and tumor invasiveness.[5] Another therapy, namely neo-adjuvant can also be used to reduce the size of the tumor before surgery.[5,6] Although breast cancer treatment continues to develop and increase cure rates, the problem of multidrug resistance (MDR) and a survival rate of only 2 – 3 years is still a major problem in the management of patients with advanced breast cancer.[6]

For the purposes of treatment options and patient prognostic assessment, tumors were classified according to their intrinsic subtypes obtained on routine histology and immunohistochemistry (IHC) examination as described in Table 1. The subtype classifications are: luminal A, luminal B, human epidermal growth factor receptor 2 (HER2)/ Neu enriched, basal-like and triple negative breast cancer (TNBC).[5,7] The subtype with hormonal receptors, luminal A, has a good prognosis and should be considered for hormonal therapy only. Luminal B with HER2 negative generally received hormonal therapy and chemotherapy, while luminal B with HER2 positive was treated with chemotherapy + anti-HER2 + endocrine therapy. The HER2 subtype has a poor prognosis with a high rate of progression, and is recommended for anti-HER2 therapy and chemotherapy. The last subtype, TNBC, has a different character and shows strong heterogeneity because it does not have expression of ER, PgR, or HER2. There is no standard therapy for this type, but chemotherapy is still recommended for patients with this subtype.[8]

Table 1. Definition of intrinsic subtypes of breast cancer.[7]

Intrinsic Subtype	Definition
Luminal A	'Luminal A-like' ER (+) HER2 (-) Low Ki67 High PgR Low risk of molecular signs (if available)
Luminal B	'Luminal B-like (HER2 negative)' ER (+) HER2 (-) Which include High Ki67, or Low PgR High risk of molecular signs (if available) 'Luminal B-like (HER2 positive)' ER (+) HER2 (+) Present Ki67 Present PgR
HER2	'HER2-positive (non-luminal)' HER2 (+) ER and PgR undetected
Basal-like	'Triple-negative' ER dan PgR undetected HER2 (-)

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; Ki67, proliferation marker.

Breast cancer is immunogenic and has several tumor antigens (tumor-associated antigens, TAAs) such as Mucin 1 (MUC 1) and HER-2 has been observed on that tumor. These properties make immunotherapy a new and very promising therapy in breast cancer therapy.[5,8].

Immunotherapy Principal

Cancer immunotherapy is the term used by the body's immune system to fight cancer cells. The principle of this therapy is to use tumor-specific immune responses to recognize abnormal proteins expressed by cancer cells, namely tumor antigens.[9] Immunotherapy basically aims to accelerate the loss of tumor cells by increasing the proliferation and activity of T lymphocytes, antigen presentation, and production of inflammatory mediators (cytokines and chemokines). Other specific goals of this therapy are to reduce the potential for metastasis, reduce the incidence of recurrence, and prevent the formation of secondary resistance.[5]

The basic principle of immunotherapy against tumor eradication is the killing of tumor cells mediated by cytotoxic T lymphocytes (CTL). Several studies have shown that breast tumors are infiltrated by immune cells, especially T lymphocytes and both show a positive correlation with a good prognosis.[5,10]

The majority of tumor antigens that can trigger an immune response are cytosolic or nuclear proteins that are endogenously synthesized which are then exposed to the cell surface by major histocompatibility complex (MHC) class I peptides. Many breast cancer tumor antigens have been identified and proven to be recognized by T lymphocytes. The tumor antigens associated with breast cancer are human epidermal growth factor receptor 2 (HER2), mucin 1 (MUC-1), carcinoembryonic antigen (CEA), human telomerase reverse transcriptase (hTERT), sialyl Tn (STn), and Wilms' Tumor. Gene (WT1).[11] T cell receptors (T cell receptors, TCR) on the surface of CD8+ cells will bind to the MHC-antigen complex and then differentiate and proliferate into cytotoxic T cells. This interaction can take place at the site of the tumor, secondary lymphoid organs, or in peripheral tissues.[9,10]

The process of antigen initiation and naive T cells also takes place due to cross-presentation of antigen presenting cells (APCs). APCs eat dead cells and extracellular peptides, and the resulting peptides are expressed on the APC surface with the help of MHC-1. Antigen presentation by APCs also stimulates expression of costimulatory molecules. Proteins B7-1 (CD80) and B7-2 (CD86) are costimulatory molecules that have been extensively studied in T lymphocytes. Some members of this protein are stimulatory and some are inhibitory to the immune response. The binding between B7-1 (CD80) and CD28 that occurs in the initial phase is stimulatory, while the binding between costimulator B7-2 (CD86) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) that occurs after T cell activation is inhibitory. Another costimulator of protein B7, programmed cell death ligand-1 and -2 (PD-L1 and PD-L2), which binds to programmed cell death -1 (PD-1) also inhibits the immune response following T cell activation.[8,10]

CTLA-4 and PD-1 have important roles in suppressive function of T cell regulation. These receptors prevent the immune response against the body's own antigens and genetic deletions that prevent autoimmune disease. CTLA-4 and PD-1 are also involved in the inhibitory response in several types of tumors that cause the immune system to fail to eradicate tumors, causing uncontrolled proliferation.[10]

Breast Cancer Vaccination

A form of stimulating an active immune response against tumors is vaccination.

Several vaccines for various types of tumors currently being developed are made from various immunogenic sources, namely whole tumor cells, tumor antigen peptides, DNA, RNA, and viruses. In addition, these components can be combined with immunoadjuvant ingredients that function to stimulate the activation of the immune system.[5]

Antigen vaccine of HER2/Neu

This vaccine model is the most potent vaccine in various published research results. The HER2 protein is a receptor protein with tyrosine kinase activity and has homology with the epidermal growth factor receptor (epidermal growth factor). HER2 is expressed in many epithelial tumors, but is overexpressed in approximately 25% of cases of primary breast cancer.[9,11] Overexpression of this protein is associated with poor prognosis in these patients. HER2 is a good target antigen because it is involved in the extracellular domain so that it can be reached and targeted by antibodies produced by B lymphocytes.[11]

There are several models of the HER2 vaccine currently under development and in different phases of clinical trials. Nelipipimut-S (NeuVax, Galenda Bipharma) is a model of the HER2 vaccine that has been extensively studied and is currently in clinical phase III in the evaluation of clinical efficacy in early-stage breast cancer (NCT01479244).[9] The tumor antigen in this vaccine, E75, is a peptide of the extracellular domain of HER2. This peptide vaccine displays a peptide bound to HLA-class 1 of the extracellular domain of the HER2/Neu protein. The E75 antigen has been shown to be immunogenic and capable of stimulating a specific CD8+ cytotoxic response to HER2. This vaccine is also currently under evaluation for its combination with GM-CSF adjuvant compounds aimed at treating tumors at various levels of HER2 overexpression. While the increase in patient outcomes (survival and immune response) with this vaccine was observed more in patients with medium or low HER2 expression.[9]

The first study using the HER2 vaccine was published in 2009. A phase I clinical trial of Lapuleucel-T (APC8024) with a combination of GM-CSF adjuvants was conducted on 18 subjects who had undergone surgery and HER2/Neu 1 status in breast cancer, ovarian cancer, endometrial cancer and colorectal. Subjects were divided and received three dose levels of the HER2 ICD protein vaccine. The vaccine is injected intradermally and monitored monthly for a year. The results obtained were good vaccine tolerance, the majority of subjects were able to produce specific T cell immunity against ICD HER2, and the vaccine dose did not predict the high T cell response.[12] Review of others ongoing clinical trials in breast cancer vaccine can be seen in Table 2.

Table 2.Ongoing breast cancer vaccine clinical trials [13]

Register Number (ID)	Vaccine Name	Study Phase	Vaccine substance	Study Participant	Study Period
NCT01479244	NeuVax (nelipepimut-s)	II	E75-GM-CSF conjugated in combination with herceptin	KP HER2 IHC 1+/2 dan nodus+	2012 – currently ongoing
NCT02297696	NeuVax (nelipepimut-s)	II	E75-GM-CSF conjugated in combination with transtuzumab	High risk BC, HER+ or nodes+	2014 - currently ongoing
NCT01390064	P10s-PADRE	I	Pan-T-Cell Epitope and neolactoseries antigen Lewis Y (LeY) and the ganglioside GD2 mimicking carbohydrate peptide (CMP) + MONTANIDE™ ISA 51 VG adjuvant	Stage IV BC	2011 - currently ongoing
NCT022229084	P10s-PADRE (Chemovax)	I/II	P10s-PADRE with chemotherapy, MONTANIDE™ ISA 51 VG adjuvant or chemotherapy and adjuvant	KP stadium I, II, atau III ER+	2014 - currently ongoing
NCT02938442	P10s-PADRE (Chemovax)	II	P10s-PADRE with MONTANIDE™ ISA 51 VG adjuvant	TNBC	2016 - currently ongoing
NCT02826434	PVX-410	Ib	tetra-peptida vaccine XBP1, CD138 and CS1 + durvalumab	Stage II/III TNBC	2016 - currently ongoing
NCT03362060	PVX-410	I	Tetra-peptide vaccine XBP1, CD138 and CS1 + pembrolizumab	TNBC	2017 - currently ongoing
NCT02960594	INO-1400, INO-9012, and INO-1401	I	A plasmid encoding hTERT	Many types of cancer and BC patients who are at high risk of tumor relapse	2014- currently ongoing
NCT02348320	-	I	Personalized polyepitope DNA	TNBC	2015 - currently

			vaccine encoding patient's own immunogenic TAAs which are selected after genome porifling of the patient's BC cells.		ongoing
NCT01730118	Ad/HER2/Neu DC	I	Autologous adenovirus HER2 – transduced DC vaccine	KP metastasis	2012 – currently ongoing
NCT00923143	-	I	HER2/Neu pulsed DC1	DCIS	2009 – currently ongoing

HER2, *human epidermal growth factor receptor* 2; BC, breast cancer; ER, *estrogen receptor*; TNBC, triple negative breast cancer; DC, *dendritic cell*; GM-CSF, *granulocyte macrophage colony stimulating factor*; hTERT, *human telomerase reverse transcriptase*.

Mucin-1 Vaccine

Mucin 1 (MUC-1) is a cell membrane glycoprotein present in various types of ductal epithelium, namely pancreas, breast, lung and gastrointestinal tract. This protein is overexpressed and glycosylated in malignant cells.[8,11] More than 70% of cancers exhibit MUC-1 overexpression which makes this antigen a potential target for immunotherapy. Although this vaccine is able to induce a specific T-cell response, the clinical outcomes achieved in this study are still unsatisfactory.[14] The largest phase III clinical trial using STnkeyhole limpet hemocyanin (KLH) vaccine (Theratope ®; Biomira, Inc., Edmonton, Canada), a conjugated STn synthetic tumor antigen in combination with an adjuvant, in 1028 patients with metastatic breast cancer found that this vaccine was well tolerated with good and able to stimulate the formation of antibodies against MUC-1 antigen, but did not provide benefits in patient outcome and survival.[15]

Preclinical studies using tumor cells with expression of MUC-1 protein or peptide antigen concluded that MUC-1 can induce a humoral immune response without inducing a cellular response. This may be due to the induction of T cell anergy by MUC-1-containing tumors. [11] Preclinical studies using tumor cells with expression of MUC-1 protein or peptide antigen concluded that MUC-1 can induce a humoral immune response without inducing a cellular response. This may be due to the induction of T cell anergy by MUC-1-containing tumors.[16]

Early clinical trials with PANVAC-V, a CEA/MUC-1/TRICOM recombinant vaccine inserted into a poxvirus vector, in patients with breast or ovarian cancer have found that this vaccine is beneficial for patients with less than three history of chemotherapy.[17]

Therapy at Immune Checkpoints

Various studies over the past decade have reported that T cell infiltration in tumors plays a role in tumor immune surveillance in humans. T cell infiltration is used as a measure of the success of therapy and also the patient's prognosis in various subtypes of breast cancer. [18,19] However, tumor cells surrounded by infiltrated T cells were still able to survive and escape T-cell immunity through the mechanisms of antigen expression deletion, T-cell regulator removal, and indoleamine-2,3-dioxygenase (IDO).[20]

Immune checkpoints are surface molecules that have a role in modulating the body's immune response, preventing autoimmunity against self-antigens, and maintaining self-tolerance. The process of T cell recruitment involves a balance between the process of stimulation with the help of co-stimulators and also inhibition in the presence of co-inhibitors. Co-inhibitors normally play an important role in maintaining immune system homeostasis, but in cancer cells these molecules become a way of escaping the body's immune response.[21]

Inhibitory antibodies that act to inhibit immune system checkpoints have shown promising potential in several studies with subjects with melanoma, bladder cancer, non-small cell lung cancer (NSCLC), and breast cancer. For breast cancer, therapies targeting immune system checkpoint co-inhibitors such as CTLA-4 and PD-1 are currently in clinical trials.[8]

Inhibitor CTLA-4

CTLA-4 is a molecule that is expressed on the surface of T cells and functions to suppress T cell activity. Signaling by CTLA-4 on CD8+ specifically will directly inhibit T cell activation.[9,10,21] CTLA-4 is also expressed by CD4+ FOXP3+ regulatory T cells and is an important immunosuppressor in these cells.[21] CTLA-4 is also able to competitively bind to the B7 ligand APCs, thereby interfering with the co-stimulatory signaling mediated by CD28 binding to B7-1.[9] Thus CTLA-4 as a checkpoint for the immune system has a crucial role in the function of CD8+ effector T cells in the early response stage to the formation of memory immune cells.

The study using anti-CLTA-4 monoclonal antibody in melanoma patients gave satisfactory results. Phase III clinical trials with Ipilimumab, a cytotoxic T-cell lymphocyte antigen 4 inhibitor, with or without the glycoprotein 100 peptide (gp100) found that there was an extension of the patient's lifespan, namely 10.0 months on average in patients receiving ipilimumab with gp100 compared to 6.4 months in patients receiving ipilimumab with gp100. the group of patients receiving only gp100 (hazard ratio for death, 0.68; $P < 0.001$). Whereas

in the group receiving only ipilimumab, the mean survival of patients was 10.1 months (hazard ratio for death compared to the gp100 group, 0.66; P = 0.03).[22] In 2011, Ipilimumab was subsequently approved by the United States FDA as the first immune system checkpoint inhibitor as adjuvant therapy for patients with cutaneous melanoma who had undergone total surgery and total lymphadenectomy in tumors with regional metastases.[21]

Currently, Ipilimumab has been widely studied for the treatment of various other cancers such as, lung cancer (non-small cell lung carcinoma, NSCLC), breast cancer, and renal carcinoma (RCC). The clinical phase 1 trial of the combination of Tremelimumab with Exemestab was conducted on 26 breast cancer patients with hormone positive response type. The side effects of this inhibitor therapy are mild to moderate (diarrhea, pruritus, constipation, fatigue) and increase the expression of co-stimulators on CD4+ and CD8+ T cells. [23]

There are two cohort studies of combined CTLA-4 inhibitors that are still ongoing. They are the combination Tremelimumab with anti-B7H1 monoclonal antibody MEDI4736 for the treatment of HER2 negative type breast cancer (NCT02536794) and the combination Ipilimumab with anti-B7H3 monoclonal antibody MGA271 in TNBC patients (NCT02381314). This inhibitor therapy still requires further investment to identify its safety profile and synergies with other therapeutic modalities.[8]

Inhibitor PD-1/ PD-L1

The major ligands for PD-1 are PD-L1 (CD274 or B7-H1) and PD-L2 (CD273 or B7-DC).[8] In contrast to CTLA-4, PD-1 inhibits the activation of T-cell immune responses at the effector stage, at the site of the reaction both in the periphery and in tumor tissue. PD1 is expressed on nearly all surfaces of several immune cells, including CD4+ and CD8+ T cells, B cells, NK cells, and regulatory T cells. Because regulatory T-cell infiltration is found in a wide variety of tumor types, inhibition of the PD1 pathway may help enhance the anti-tumor immune response by reducing the number and/or suppressing the activity of intra-tumor regulatory T cells.[24] Although clinical experience with PD1 antibodies is currently less than with CTLA4 antibodies, preliminary results look very promising. Resume of the current study of CTLA-4 and PD-1 inhibitors is shown in Table 3.

The first phase 1 clinical trial with this inhibitor was a clinical trial using a single anti-PD-1 antibody (MDX-1106) in 39 metastatic cancer patients. The results obtained in the form of good tolerance and showed anti-tumor activity. Some cases even experienced tumor regression.[25] In 2014, for the first time a PD-1 target therapy, Nivolumab (Opdiva®, Bristol-

Myers Squibb) was approved by the United States FDA. This therapy was developed purely from human IgG4κ monoclonal antibody. Nivolumab is approved as first-line therapy for untreated melanoma and has been shown to have no mutations in BRAF. More recently, nivolumab has also been approved as adjuvant therapy in stage III/IV melanoma in patients who have undergone total surgery.[21]

Table 3. Several ongoing clinical trials of CTLA-4 and PD-1 inhibitors.[8]

Register Number (ID)	Formula	Study Phase	Study participant
CTLA-4			
NCT02536794	MEDI4736 + Tremelimumab	II	HER –
NCT02381314	MGA271 + Ipilimumab	I	TNBC
PD-1			
NCT02661100	Pembrolizumab + CDX-1401 + Poly ICLC	I/II	TNBC advanced stage
NCT02453620	Entinostat + Iplimumab + Nivolumab	I	HER –
NCT02129556	Pembrolizumab	I/II	HER2 + (Transtuzumab resistance)
NCT02309177	Nab-Paclitaxel + Nivolumab + Gemcitabine + Carboplatin	I	BC
NCT02404441	PDR001	I/II	TNBC
NCT02555657	Pembrolizumab + Capecitabine + Eribulan + Gemcitaine + Vinorelbine	III	TNBC

HER2, *human epidermal growth factor receptor* 2; BC, Breast Cancer; TNBC, *triple negative breast cancer*

Atezolizumab (Tecentriq®), an IgG1κ monoclonal antibody, is the first anti-PD-L1 monoclonal antibody approved as an immune checkpoint inhibitor therapy. This drug is approved for use in cases of localized or metastatic urothelial cancer and NSCLC.[21]

PD-L1 protein expression was detected in 20-30% of breast cancer patients, especially in the TNBC type. Animal model studies and clinical trials show that PD-1 and PD-L1 inhibitors have potential for breast cancer therapy. In a non-randomized phase 1 trial of 32 recurrent/metastatic PD-1 positive TNBC patients showed that pembrolizumab monotherapy was well tolerated and only 15.6% of patients had single symptomatic side effects. These results are similar to those of a combination therapy study between atezolizumab and nab-paclitaxel in metastatic breast cancer with positive PD-L1, ER, and negative profiles. HER2. These results then became the basis of a phase 3 clinical trial aimed at evaluating the combination therapy of Atezolizumab and Nab-paclitaxel in TNBC metastases that are still ongoing. (NCT02425891).[8]

It is very important to find an effective therapy in TNBC breast cancer with

significant therapeutic activity. This is because this type of breast cancer is easy to metastasize and is recurrent. Until now there is no ideal treatment protocol for TNBC, so many patients receive different types of therapy to treat the nature of this type of breast cancer.

Conclusion

Scientific evidence regarding tumor antigens and co-stimulatory compounds capable of activating anti-tumor immune responses, makes immunotherapy a promising therapy for success in preventing cancer recurrence and metastasis in the future. However, the current application of immunotherapy for breast cancer therapy is still far from satisfactory. Currently, several types of breast cancer vaccines are still in the clinical research stage. The immune system checkpoint inhibitor therapy in combination with other therapies in several studies has shown good results, although it has not been able to completely inhibit tumor regression. The current massive development of molecular biology and genomics is expected to perfect this therapeutic model product so that it can reduce the mortality rate of this disease in the future.

Conflict of Interest

Nothing to declare

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None

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Nothing to declare

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CASE REPORT **Open Access**

The Role of Chest Radiography to Diagnose Large Pericardial Effusion in Woman 66 Years Old With Malignancy : *Hiding Pericardial Effusion*

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ABSTRACT

Introduction: Pericardial effusion refers to an increase in fluid accumulation in the pericardial cavity. This pericardial fluid acts as a lubricant between the layers of the pericardium. We report a case of pericardial effusion, which was significant but not detectable on conventional chest radiographs.
Case: A 66-year-old woman with lung adenocarcinoma accompanied by large pericardial effusion without sign of impending tamponade. The diagnosis of pericardial effusion was mainly based on echocardiography, where there is a large pericardial effusion but without signs of cardiac tamponade, and the patient then underwent pericardiocentesis. Previously, the patient had undergone two examinations with two different imaging modalities, namely CXR and chest CT scan, where on the CXR results, the patient only showed cardiomegaly.
Discussion: There are four parameters suggestive for assessing a pericardial effusion, namely enlargement of the heart silhouette, pericardial fat stripe, left dominant pleural effusion, and an increase in the transverse diameter of the heart compared to the previous chest X-ray. This parameter is obtained not only based on the position of the photo taken but requires another position, whereas, in this patient, only CXR was performed with the posteroanterior position.
Conclusion: When there are complaints of progressive shortness of breath in individuals with an underlying disease that may cause pericardial effusion, then the CXR examination cannot be used as a reference when there are no radiographic signs that point to pericardial effusion because CXR has a low diagnostic value in assessing the presence of pericardial effusion.

Keywords : Chest Radiography, Malignancy, Pericardial Effusion

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Introduction

Pericardial effusion refers to an increased accumulation of fluid in the pericardial cavity where the amount is only between 15 and 50 ml of serous fluid under normal conditions.[1] This pericardial fluid is a lubricant between the layers of the pericardium.[2] Fluid accumulation that occurs can be in the form of exudate, transudate, or sanguine. In general, the cause of pericardial effusion can be from infection, rheumatology, neoplasm, trauma, cardiac, vascular, idiopathic, and other causes1, which then broadly etiology can be grouped into inflammatory causes and causes non-inflammatory.[3]

One study conducted from 2006 to 2016 in Mexico to assess the prevalence of pericardial effusion in systemic diseases found that the enormous volume of pericardial fluid accumulation was in patients with neoplastic etiology. However, neoplasms themselves were not the most common etiology of pericardial effusion.[2] The 2015 European Society of Cardiology (ESC) guideline on managing pericardial disease states that in developing countries, neoplasms account for 10-25% of cases as the etiology of pericardial effusion.[3]

Pericardial effusion is a common clinical condition in daily practice in symptomatic and asymptomatic patients. A clinician needs the ability to make a diagnosis before it develops into a life-threatening condition such as cardiac tamponade, particularly in areas with limited imaging modalities. This case report aims to describe the types of radiological modalities that can be used in diagnosing pericardial effusion, especially conventional radiography so that it can be seen whether a simple modality is sufficient to establish a pericardial effusion.

Case

The pulmonology division consulted a 66-year-old woman diagnosed with lung adenocarcinoma stage T4N2M1c and pericardial effusion. The current patient complains of shortness of breath that had been felt for two months which has worsened in the last week. There was dyspnea on effort and paroxysmal nocturnal dyspnea. There was a history of previous intermittent shortness of breath for the last two years. There had been a weight loss of approximately 15 kg in the last nine months. The patient had a history of breast cancer three years ago and had a mastectomy. The patient had been diagnosed with lung adenocarcinoma and had undergone oral chemotherapy with IRESSA (gefitinib) since 2021 and stopped in March 2022. The patient had also previously undergone nine cycles of

chemotherapy, but the patient stopped at the patient's wish. The patient had a history of confirmed COVID-19 in March 2022 and passive smoking for the last 30 years.

On physical examination, he was conscious with a weight of 48 kg, a height of 163 cm (Body Mass Index of 18.07 kg/m2), blood pressure 110/80 mmHg, pulse 105 times per minute regular, breathing 24 times per minute, body temperature 36.5 Celsius, and oxygen saturation 98% with nasal cannula 4 liters per minute. On physical examination, the thorax was symmetrical, the vocal fremitus decreased in the right mediobasal region, dull percussion on the right hemithorax as high as ICS IV to the base, vesicular breath sounds, and decreased impression in the right mediobasal region of the right hemithorax, no rhonchi and wheezing were found. Electrocardiographic examination found rhythmic sinus rhythm, heart rate of 107 beats per minute, regular, low voltage limb and precordial leads, and electrical alternans (Figure 1).

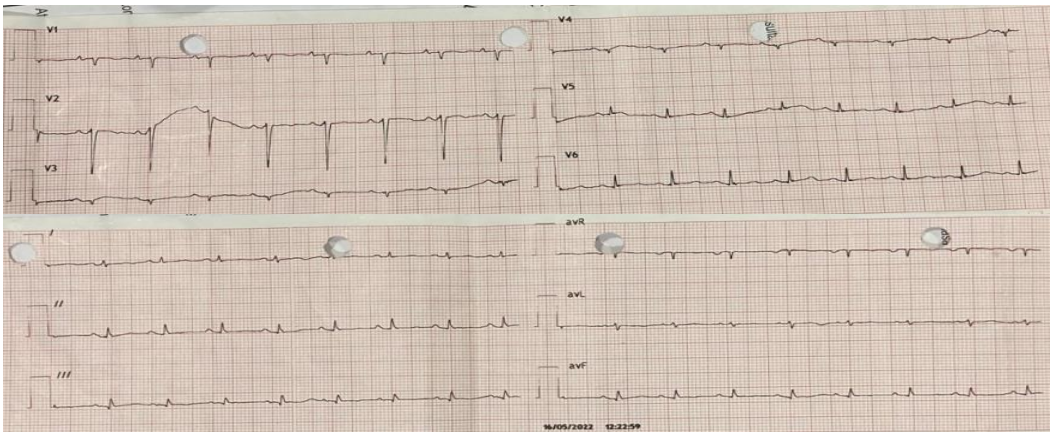

Figure 1. Electrocardiography finding of the patient

From the chest x-ray examination, the impression of a soft tissue mass of the right lung, bilateral pulmonary fibrosis, thickening of the right lung minor fissure, right pleural effusion, and cardiomegaly with dilatation et atherosclerosis of the aorta was obtained (Figure 2). Then, the patient underwent a multislice computed tomography (MSCT) scan with the results of a right lung mass with tumor metastases to bone and liver, bilateral pulmonary fibrosis, right bilateral pleural effusion, pericardial effusion, and atherosclerosis of the aorta (Figure 2). When consulted to the Cardiology division, bedside echocardiography was performed with the results of large pericardial effusion with swinging heart and without signs of impending cardiac tamponade, normal left and right ventricular systolic function (eyeballing), no right atrial and right ventricular collapse, and negative of IVC plethora (Figure 3).

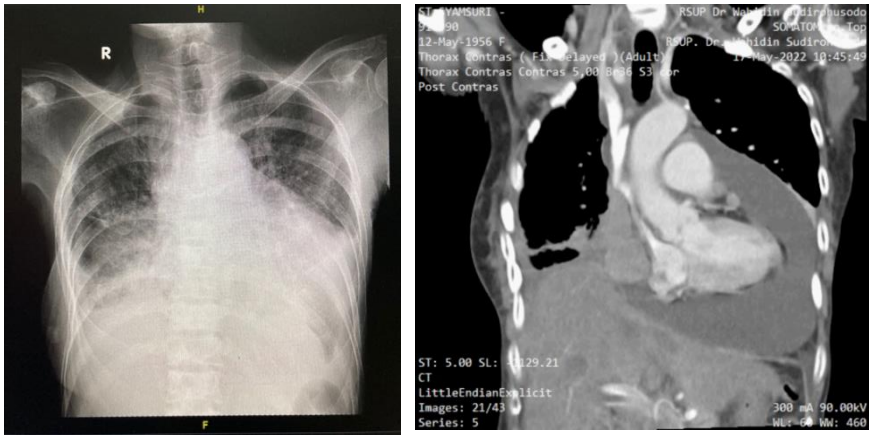

Figure 2. The results of the chest X-ray (left) and chest MSCT (right) from the patient.

Based on the history, physical examination, and supporting examinations, our patient was diagnosed with Large Pericardial Effusion without signs of Impending Cardiac Tamponade and planned for Pericardiocentesis with an aspiration of 300 ccs of pericardial fluid in which fluid The pericardial discharge is hemorrhagic and recommended for aspiration of pericardial fluid every 8 hours from the patient.

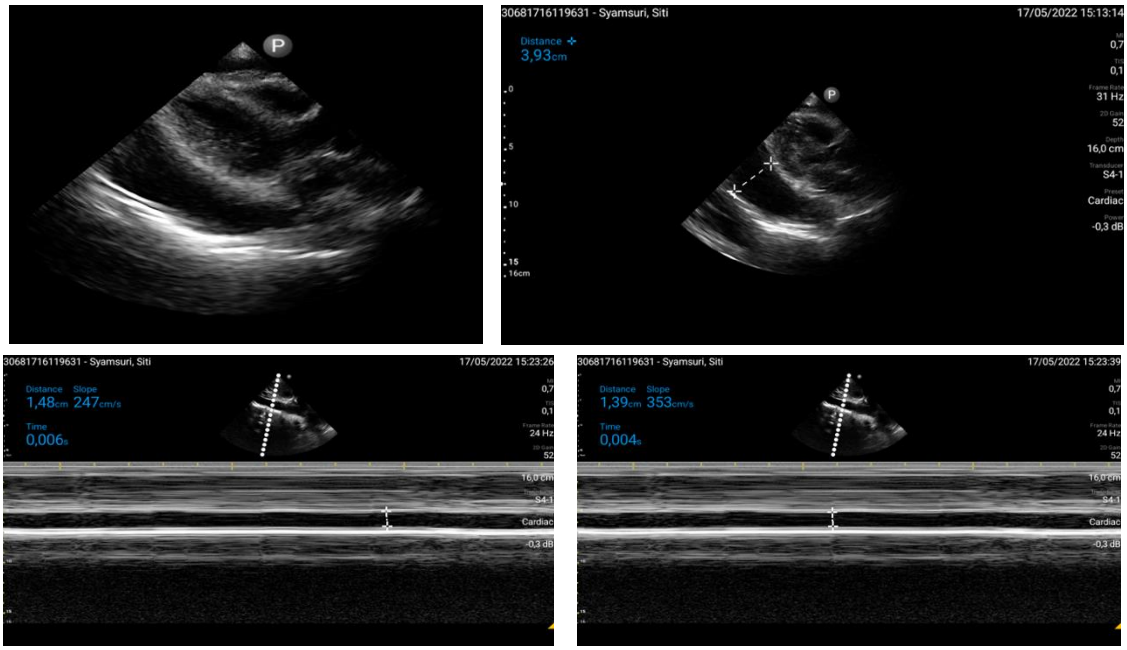

Figure 3. Pre-pericardiocentesis echocardiography in the patients.

Discussion

Lung cancer is the leading cause of death in cancer cases.[4] It was stated that the most cardiovascular complications in patients with lung cancer undergoing radiation therapy (RT) to the thorax were pericardial effusion and cardiac tamponade. In an autopsy study of patients with a history of radiation therapy, 70% had pericardial damage on the thorax.[5]

The pericardium is an avascular fibrous sac that encloses the heart and major blood vessels such as the proximal pulmonary trunk, ascending aorta, and distal to the superior and inferior vena cava. [6.7] The pericardium consists of two layers, namely the fibrous and serous layers. Then the serous layer consists of the visceral and parietal layers.[6] The visceral layer contains a single layer of mesothelial cells attached to the epicardium with a thickness of <1 mm in producing pericardial fluid. The parietal layer is a fibrous layer with a thickness of <2 mm with the main content is a small amount of collagen and elastin tissue which gives little elasticity to the pericardium so that the pressure-volume curve of the pericardium does not run linearly.[7,8]

This patient has had a primary disease, namely lung cancer, since two years ago. The patient had also received oral and parenterally chemotherapy but did not undergo the treatment routinely. One of the most common cardiovascular complications in patients with lung cancer is pericardial effusion, where malignancy is the cause of pericardial effusion in 10-25% of cases.[3]

In chronic conditions, the accumulation of pericardial fluid will occur gradually over a certain period before hemodynamic instability occurs. At this time, the patient will not show acute circulatory failure, but the symptoms that arise are shortness of breath that is getting worse, as in this patient, pericardial effusion due to an ongoing chronic condition, namely lung malignancy.[9] In this chronic condition, there will be an increase in the accumulation of pericardial fluid slowly. The pericardial membrane stretches to accommodate this increase in pericardial fluid volume without significant changes in pericardial pressure, and the patient is asymptomatic until the stretch of the pericardial membrane reaches its limit, causing symptoms..[8,10]

In this patient, it can be said that she is not in a state of cardiac tamponade because he did not meet the cardinal symptoms and signs of cardiac tamponade, i.e., hypotension, pulsus paradoxus, increased central venous pressure (in which this patient obtained DVS R + 2 mm Hg), and distant heart sounds on chest auscultation.[3] However, in this patient, the physical examination revealed the presence of tachycardia.

Patients are admitted with complaints of shortness of breath in the emergency department, where shortness of breath is a common symptom of cardiovascular and respiratory diseases.[9] Routine examinations such as electrocardiography (ECG) and chest X-ray (CXR) can be performed to help establish a diagnosis.[1]

On ECG examination, this patient found the presence of low voltage limb and precordial leads, and electrical alternans. The ECG can vary from normal to non-specific ST-T segment changes in small pericardial effusions.[1] The ECG images found in this patient are appropriate for cases of pericardial effusion because it is said that the characteristic ECG in large pericardial effusions may be low QRS voltage, PR segment depression, and electrical alternans. These ECG findings are said to be specific but less sensitive for pericardial effusion, so the 12-lead ECG is a less supportive modality in diagnosing pericardial effusion.[9]

Various imaging modalities can be performed to establish a pericardial effusion, including Chest X-Ray, CT scan, Magnetic Resonance Imaging (MRI), or Echocardiography. The diagnosis of pericardial effusion is made based on echocardiography which can semiquantitatively assess the size and hemodynamic effects of the pericardial effusion.[3] Based on the European Society of Cardiology (ESC) guidelines on the management of pericardial disease, transthoracic echocardiography examination is the recommended examination in diagnosing pericardial effusion (Class I Recommendation, level C).

On CXR examination, the pericardial layer commonly will not be seen.[11] When a pericardial effusion occurs, the accumulation of pericardial fluid will be seen on the CXR image but will still not be seen if the accumulation of fluid that occurs is <200 ml.[12] In one study, the signs of pericardial effusion based on CXR were enlarged heart silhouette, pericardial fat stripe, left dominant pleural effusion, and increased transverse diameter of the heart compared to the previous chest radiograph.[13]

Left pleural effusion is the sign most associated with pericardial effusion, while right pleural effusion is more associated with the presence of heart failure. This left pleural effusion is a specific sign of pericardial effusion. However, it is not sensitive because this pericardial effusion will still be associated with pericardial effusion even though it is found in individuals with lung disease and pleural disease. Pericardial fat stripe is a sign found only in large pericardial effusions, so it is said to have a sensitivity of up to 50% in this group, and the sensitivity will decrease as the amount of fluid accumulation in the pericardial cavity decreases.[13]

It is argued that an enlarged cardiac silhouette and an increase in the transverse diameter of the heart compared to the previous CXR are signs of pericardial effusion. This sign can be said to suggest a pericardial effusion if it excludes the presence of cardiac disease in the individual. The presence of underlying heart disease that causes an enlarged heart chamber can also be seen as an enlarged heart image on radiography.[13]

In the frontal view, an enlarged heart image will be obtained, calculated based on the Cardiothorax Ratio (CTR), which is >50%.[12] This image gives a globular shape with a symmetrical enlargement of the heart contour called the "water bottle sign" due to a considerable accumulation of fluid in the heart. Pericardial cavity so that it gives a water bottle or "flask-shaped," namely a pumpkin-like heart appearance.[8,10,12,14] The "water bottle sign" will appear in 68% of patients with large pericardial effusions (>500 ml) where the results of echocardiography show a pericardial effusion >2 mm.[13]

In pericardial effusion with posterior expansion, there can be an increase in the cranial angle formed by the right and left main bronchial > 90 degrees. On the lateral view, there is a "bulge sign" on the posteroinferior and a loss of retrosternal space on the anterosuperior. In addition, it can also be found the presence of pericardial fat, which visualizes the fluid that is between epicardial fat and pericardial fat, which is called the "Oreo cookie sign" or "sandwich sign" or "Retrosternal fat pad sign," where epicardial fat and pericardial fat will give an image of a high density. In contrast, the pericardial fluid will give an image of intermediate density. [12,15] This image will be seen anteriorly due to adipose tissue being more attached to the right ventricle. [12] On the lateral view, a "double-lucency sign" can also be found.[9] Further, by using density differences, pericardial fluid and myocardium had distinct features, but this method is limited to transudate or chylous fluids with low density so that they can be distinguished from myocardial density.[12]

From all radiological images obtained on CXR, it is said that no sign can distinguish individuals with pericardial and without pericardial effusion. Of the four radiological signs of CXR mentioned above, enlargement of the heart silhouette gives a reasonably good sensitivity value of 71% but has a low specificity value of 41%. While the other three signs, namely left pleural effusion, pericardial fat stripe, and increased transverse diameter of the heart, gave the opposite value, namely 78% for specificity and a low sensitivity value of <70%. When viewed from the size of the pericardial effusion, although there were no radiographic signs on CXR indicating their size, left pleural effusion and pericardial fat stripe were said to be able to show moderate to large pericardial effusion even though these two signs had low sensitivity but have a specificity value of > 91% and an accuracy of > 70%. On this basis, CXR is said to have a low diagnostic level in establishing pericardial effusion.[13]

This patient only found cardiomegaly characterized by CTR exceeding 50%, which can occur in pericardial effusion but can also occur in various conditions other than pericardial effusion, such as enlargement of the heart chambers due to cardiac structural disorders. No

water bottle sign was found, which is a sign of pericardial effusion, possibly due to pleural effusion in the right hemithorax, according to what was found on physical examination, namely dimness on percussion of the right hemithorax as high as ICS IV so that the right border of the heart to assess the presence of a water bottle sign became obscured. However, this sign is said to be present in 68% of patients with large pericardial effusions and echocardiography >2 mm. In addition, there was a right pleural effusion in this patient. Right pleural effusion was more associated with the presence of heart failure. However, in this patient, it was suspected that it was due to a malignant process that occurred in the right lung, while what was said to be associated with pericardial effusion was left pleural effusion even though it was said to be Left pleural effusion and pericardial fat are not diagnostic for pericardial effusion.[13] Therefore, based on the CXR finding, it is not said to be a true pericardial effusion on other imaging modalities in this patient, revealing a large pericardial effusion (> 500 ml). This finding can happen because the CXR image has a low diagnostic level in establishing a pericardial effusion,[13] so in this patient, an imaging examination with other modalities such as echocardiography was performed.

An echocardiography examination will visualize the pericardial effusion as an echo-free space surrounding the heart.[7] The presence of cardiac chamber collapse is a sign that can be found before hemodynamic failure.[8]

Based on the size, the pericardial effusion can be classified into small (50-100 ml), moderate (100-500 ml), and large (> 500 ml), in addition to other classifications based on the onset, distribution, and composition of the accumulated pericardial fluid.[3,11] In trivial pericardial effusion, this accumulation of pericardial fluid will only be seen in the posterior region of the heart, namely behind the left ventricle in the oblique sinus, as well as in small pericardial effusions. However, trivial pericardial effusion can only be seen during the systolic phase, while small pericardial effusion can be seen in both the systolic and diastolic phases.[7,11] If there is an increase in the accumulation of pericardial fluid to > 100 ml (moderate epicardial effusion), the spread of pericardial fluid will occur circumferentially so that it can be seen both anteriorly and posteriorly to the heart. i.e., the free movement of the heart in the pericardial cavity.[10]

Based on the results of echocardiography from this patient, it was found that there was an accumulation of pericardial fluid with a size of 3.93 cm (39 mm) which was classified as a large pericardial effusion which was estimated to be >500 ml of accumulated pericardial fluid. In this patient, the accumulation of pericardial fluid occurs slowly, as evidenced by the

complaint of shortness of breath that has been felt for two months gradually.[11] In addition, the presence of lung cancer experienced two years ago is the etiology of a pericardial effusion, where it is said that neoplasm is one of the causes of chronic pericardial fluid accumulation. (hypotension, increased central venous pressure, and distant heart sounds) were not found.[8]

Based on echocardiography findings in this patient, there was no sign of cardiac tamponade as mentioned above, so this patient was diagnosed with Large Pericardial Effusion without sign of impending tamponade. It is said that pericardial effusion will not always show an echolucent image on echocardiography due to the presence of fibrin/clot, protein, chyle, tumor cells, and bacteria.[11] Therapy for pericardial effusion with known etiology is required to treat the underlying disease as the cause of the pericardial effusion.[3,10] In the European Society of Cardiology guidelines for the management of pericardial effusion, it is stated that pericardiocentesis is an invasive therapy performed on large pericardial effusions that have not been successfully treated pharmacologically and are also the treatment of choice for pericardial effusions with a malignant etiology (Class I Recommendation, Level C).[3]

Conclusion

No single radiological sign on CXR examination can be used as a diagnostic standard for pericardial effusion. However, this patient found cardiomegaly, which has a sensitivity of 71% but low specificity of 41%, so the signs obtained have no diagnostic value but only have predictive value for pericardial effusion. Therefore, CXR examination cannot be used as a reference when there are no radiographic signs suggesting pericardial effusion regarding its low diagnostic value in assessing the presence of pericardial effusion.

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CASE REPORT **Open Access**

General Seizures Due to Brain Abscess Causa Suspected Intracranial Tuberculosis at Prof Aloei Saboe Hospital Gorontalo

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ABSTRACT

Introduction: Seizures are a severe clinical condition with complications of brain abscess. This report will describe the rare occurrence of generalized seizures due to Mycobacterium tuberculosis (MTB) brain abscess.
Case: Male, 57 years old, admitted to the emergency department with two episodes of generalized seizures one hour before admission. The patient had a history of pulmonary tuberculosis during four months of treatment and was treated with an anti-tuberculosis fixed drug combination (FDC) 3. The patient was in a state of delirium and had lower extremity weakness. The chest radiograph shows a multifocal patchy opacity in the right upper lobe with thickening in the right pericardium. Pre-Contrast MSCT-Scan of the brain showed multiple hypodense lesions in the left frontal lobe, right frontoparietal, left basal ganglia, and pons. Post-contrast shows multiple low-attenuation, oval-shaped lesions with peripheral enhancement (double rim sign) with vasogenic edema. Finally, the patient was diagnosed with a tuberculous brain abscess.
Discussion: CNS tuberculosis is a rare cause of seizures and is often followed by a history of pulmonary tuberculosis. Tuberculosis appears on the Contrast MSCT Scan Brain as an avascular mass lesion of low density and sometimes more significant than expected around cerebral edema. End-stage tuberculosis is well encapsulated and has peripheral ring enhancement with vasogenic edema.
Conclusion: Pre-Post Contrast Brain MSCT is the diagnostic imaging of choice for suspected tuberculous brain abscess.

Keywords: Brain Abscess; MSCT-Scan; Tuberculosis

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Introduction

All body organs, such as the central nervous system (CNS), can be infected by tuberculosis. The incidence of extrapulmonary CNS is around 10%, and one of the causes is Tuberculosis Abscess.[1,2,3,4] CNS tuberculosis is a rare cause of seizures and is often followed by a history of pulmonary tuberculosis. Approximately 1% of all TB patients develop CNS TB, which usually presents as meningitis. A less common form of CNS TB, intracranial tuberculoma, usually affects immunocompromised patients.[5] Seizures are a neurological emergency as a clinical manifestation of complications of bacterial brain abscess, both early and late.[5] This paper presents a rare case of generalized seizures due to a tuberculous brain abscess.

Case

A 57-year-old man had two episodes of generalized seizures one hour before hospitalization. The patient had a history of pulmonary tuberculosis during four months of treatment and was treated with FDC 3. A general examination showed normal vital signs. The patient was in delirium on physical examination and had decreased inferior motor strength. The chest radiograph showed a multifocal patchy opacity in the right upper lobe with right pericardial thickening (Figure 1).

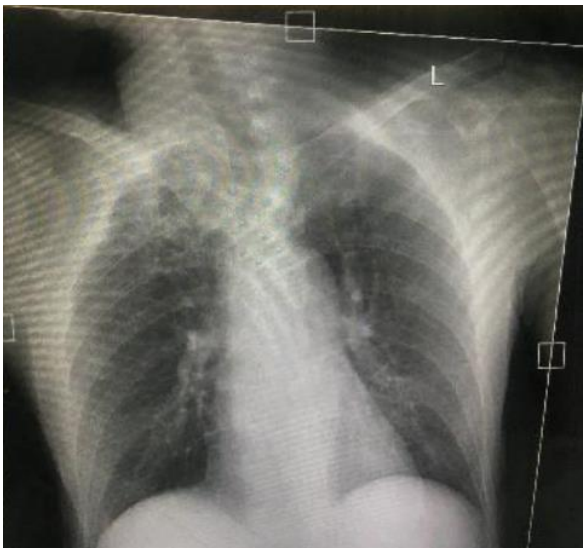

Figure 1. The results of the chest X-ray examination of the patient

Pre-Contrast Head MSCT Scan showed multiple hypodense lesions in the left frontal lobe, right frontoparietal, left basal ganglia, and pons (Figure 2). Post-Contrast Head MSCT Scan showed multiple low-attenuation oval-shaped lesions with peripheral enhancement

(double rim sign) with vasogenic edema (Fig. 3). The patient was diagnosed with Generalized Seizure and Inferior Paraparesis due to Tuberculosis Brain Abscess.

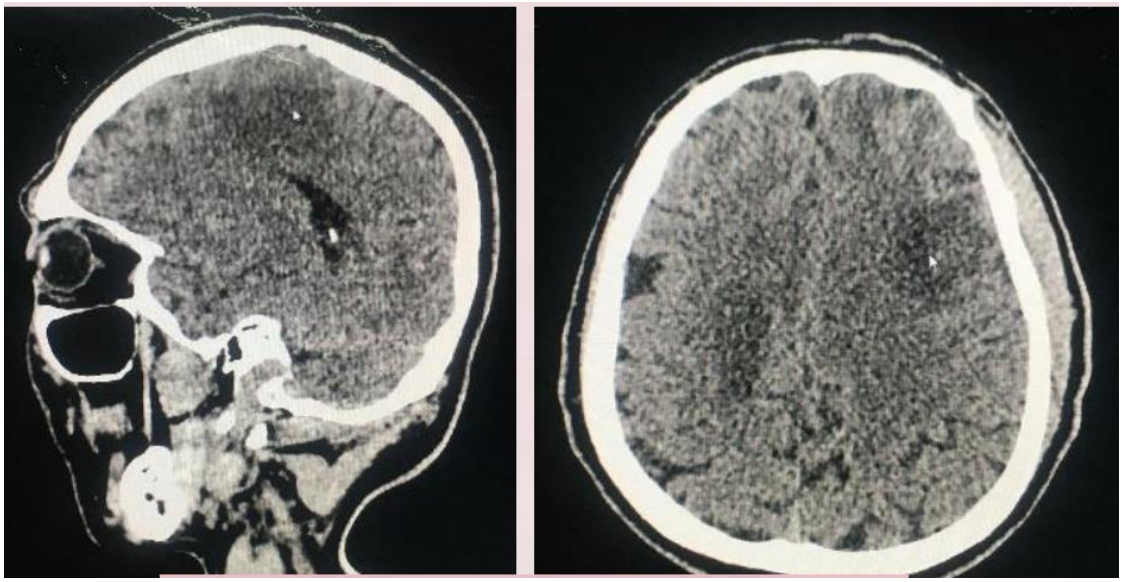

Figure 2. The results of the Pre-Contrast Head CT-scan in the patient.

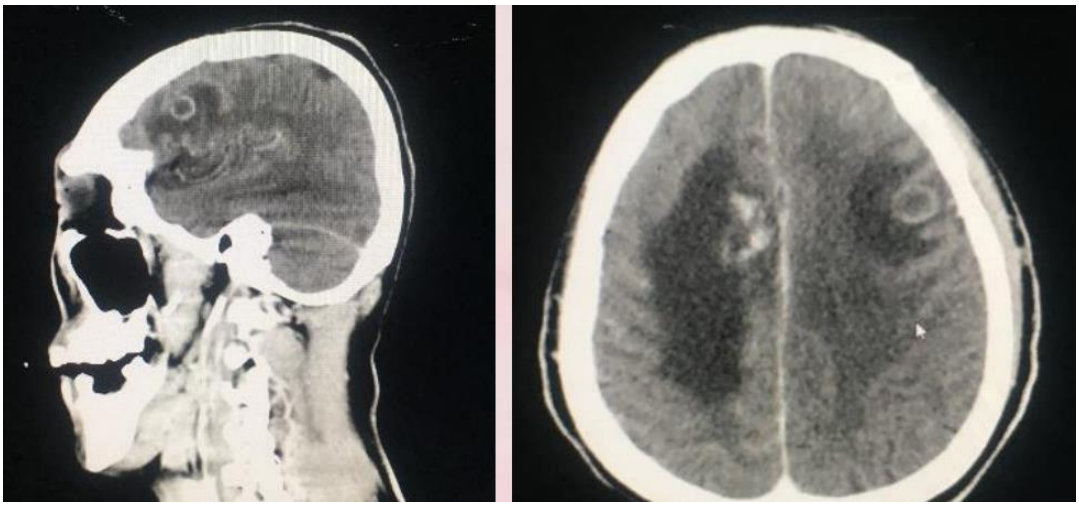

Figure 3. The results of the Post-Contrast Head CT-scan in the patient.

Discussion

CNS tuberculosis is a rare cause of seizures and is often followed by a history of pulmonary tuberculosis. Approximately 1% of all TB patients develop CNS TB, which usually presents as meningitis. A less common form of CNS TB, intracranial tuberculoma, usually affects patients with compromised immune systems.[6]

Tuberculosis brain abscess is a much rarer manifestation. They originate from the hematogenous spread of *Mycobacterium tuberculosis* (MTB) from the lungs to the brain

parenchyma, creating well-demarcated granulomatous foci. These foci may enlarge and cause a localized mass effect without rupturing into the subarachnoid space.[6]

Tuberculosis appears on contrast MSCT Scan Brain as an avascular mass lesion of low density and sometimes more significant than expected around cerebral edema. End-stage tuberculosis is well encapsulated and has peripheral ring enhancement with vasogenic edema.[2,3]

It is often difficult to identify the clinical manifestations of a tuberculous brain abscess in an emergency. The clinical signs of tuberculosis are variable and non-specific, and the radiological features are often similar to those of other infectious and non-infectious disorders. Although intracranial biopsy and histopathology are technically required to diagnose intracerebral tuberculoma, these procedures are often impractical because of the invasiveness and proximity of the lesion to structures critical to survival and the risk of meningitis from accidental spread through the subarachnoid space.[7,8] This case is a challenge for the radiologist in the setting of generalized seizures in a patient with a tuberculous brain abscess and an unknown immune status.

Conclusion

Tuberculous brain abscesses are rare, and diagnosing the disease is challenging for radiologists. Pre-Post Contrast Brain MSCT may be useful as diagnostic imaging in this case.

Conflict of Interest

We do not have any potential conflict of interest

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REVIEW ARTICLE **Open Access**

Retinal Laser Photocoagulation

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ABSTRACT

Background: Panretinal photocoagulation (PRP) is the standard gold therapy to prevent vision loss in severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).
Contents: Photocoagulation is a therapeutic technique using a solid light source to coagulate tissue. This light energy is absorbed by the retinal tissue and converted into thermal energy. This energy then causes the abnormal blood vessels in the retina to shrink and disappear. It takes approximately 6-8 weeks for complete shrinkage of blood vessels.
Conclusion: Laser retinal photocoagulation is the standard therapy in diabetic retinopathy patients. By causing thermal lesions of the pathological retinal vessels, the expected outcome can be achieved in 2-3 months of therapy.

Keywords: Diabetic Retinopathy, Laser, Panretinal Photocoagulation

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Introduction

Panretinal photocoagulation (PRP) is the standard gold therapy for preventing vision loss in severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Laser photocoagulation provides a neovascularization regression effect to prevent and stop the progression of diabetic retinopathy. The laser beam used can cause minor burns on the peripheral retina. This burn causes abnormal blood vessels to shrink and disappear. It takes approximately 6-8 weeks for complete shrinkage of blood vessels.[1,2,3]

Laser Mechanism of Action

Light Amplification by Stimulated Emission of Radiation (LASER) is different from ordinary light in that it radiates in all directions according to the path of the light. Ordinary light also consists of a collection of light waves, each of which has a different wavelength, whereas laser light travels as parallel rays and almost does not spread. Laser light is a type of beam that is monochromatic and coherent.[4]

The process of producing laser light is called stimulated emission, where this process reproduces light waves. A material will usually release light through spontaneous emission. One of the electrons in the atom will absorb energy. Meanwhile, the atom stores energy in an excited state, and if the electrons release excessive energy, then spontaneous emission will occur. If a wave is released by an excited atom and hits another atom, then this second atom will be stimulated to release energy so that a second wave is formed which runs parallel and the same as the first wave, and if these two waves stimulate the other atom it will form an abundant of a coherent beam of light. The atoms will release photons that are visible as laser light.[4,5]

Laser Beam Effect

Direct and coherent laser beam radiation causes the beam to focus on a single point. The monochromatic laser beam can have different wavelengths to produce the desired beam effect on specific tissue layers. Laser effects in surgery include thermal, ionizing, and photochemical effects.[5,6]

Thermal effects can be in the form of photocoagulation and photo vaporization effects. The photocoagulation effect will occur in conditions where an increase in temperature of about 10ºC to 20ºC will cause the targeted eye tissue coagulation. This photocoagulation effect is often used in retinal laser surgery. The amount and speed of temperature depend on the target tissue's location and the absorption rate of the wavelength used. The photo vaporization effect will occur when laser energy increases the temperature of the cellular and extracellular fluids to reach 100ºC, resulting in heating and tissue

vaporization. Usually, the light used has a wavelength of weak penetration, so most of the laser energy is absorbed superficially and causes tissue tearing due to tissue vaporization. The ionization effect will occur if the beam with very high radiation and short exposure time in a small spot will produce electrons that get energy from the target tissue molecules and, in the end, form a free electron and ion plasma called plasma. The rapid expansion of the plasma causes sound waves and vibrations accompanied by stretching of the tissue, incision of the tissue, and then producing photodisruption of pigmented tissue or absorption of laser light. Transparent tissue can be torn in this situation, for example, in the NdYAG Laser (neodymium-doped Yttrium Aluminum Garnet Laser). Photochemical effects can occur through intense laser energy, which will occur when the photon energy is high enough. The energy of the photon will increase when the wavelength is short. The photochemical effect has been used in experiments using red light (630nm) to generate cytotoxic free radicals in tumors. [6]

Principal of Laser Retinal Photocoagulation

Photocoagulation is a therapeutic technique using a solid light source to coagulate tissue. The light energy is absorbed by the target tissue and converted into thermal energy. When the tissue temperature exceeds 65ºC, tissue protein denaturation and coagulative necrosis will occur. Most surgeons currently perform laser tissue photocoagulation using a light spectrum between 400-780 nm. Green, red, yellow, and infrared rays are commonly used for the posterior segment. This irradiation system can be transpupillary using a slit-lamp, indirect ophthalmoscope, endophotocoagulation during vitrectomy surgery, and transscleral using direct contact probing. [4]

The effectiveness of light in causing photocoagulation depends on the ability of the light to penetrate the ocular medium and how well pigments absorb the light in the target tissue, such as melanin, xanthophyll, and hemoglobin pigments. Melanin is the most important pigment in the eye and is present in the RPE cells and the choroid. Melanin absorbs light in the retinal pigment epithelium (RPE), the primary energy source in retinal photocoagulation. Melanin is very good at absorbing green, yellow, red, and infrared light. Xanthophylls are yellow pigments found in the retinal layer of the macula. Xanthophylls become a heat source when a photocoagulation laser with blue argon light is fired close to the fovea. Xanthophylls are very good at absorbing blue light, while yellow and red light is absorbed minimally. Hemoglobin is very good at absorbing argon rays and is a source of heat energy when most of the laser energy is concentrated in the blood vessels. Hemoglobin quickly absorbs blue, green, and yellow light but a small amount of red light. [4,5]

The choice of light wavelength depends on the therapy's goal. Based on the ability to absorb light from the tissue pigments, the surgeon will choose to achieve photocoagulation in the target tissue without damaging adjacent normal tissue. In addition, factors that must be considered are the area, including the depth and diameter, for effective coagulation to occur, which is directly related to the intensity and duration of radiation. Laser parameters such as spot size, duration, and power also depend on the refractory medium's clarity and the fundal pigmentation level.[4]

The selection of the optimum wavelength depends on the absorption spectrum of the target tissue. Generally, lasers that are often used for retinal photocoagulation are Argon rays, Krypton Yellow, and Diodes. Argon emits blue-green light at about 488-515nm. This light consists of 70% blue and 30% green. Argon can be converted to emit only green light by using a filter. As for Krypton Yellow light, emitting a beam of about 577nm, it is often used because of its ability to coagulate red lesions directly. In comparison, the Diode beam emits infrared at 780-950nm. [5]

Laser Parameters, Systems and Instruments

The three main parameters of the laser beam that need to be considered are spot size, power settings, and exposure time. Spot size varies between 50-500µm. It is essential to know that the smaller the spot, the greater the energy. Therefore, the power level must be reduced when changing the spot size to a smaller one. For focal therapy, the spot size is usually 50-100µm, while for pan-retinal photocoagulation, the spot is between 200-500µm. In addition, the power settings are energy power ranging from 0 to 3 W (0-3000mW). A highly pigmented fundus requires less energy when compared to a less pigmented fundus to produce the same combustion. Finally, the exposure time usually varies from 0.01 to 5 seconds. However, in some cases, intraocular tumor therapy requires a longer exposure time.[5,6]

Laser therapy can be delivered in three ways, namely slit lamp biomicroscope, laser indirect ophthalmoscope (LIO), and endolaser probe. Slit-lamp remains the method of choice in most cases, particularly in cases requiring precise laser application, such as photocoagulation of the macula. Contact lenses are used when using the slit lamp method, which functions as image magnification accompanied by the initial action of administering local anesthesia. LIO has been widely used since 1981, mainly for photocoagulation of peripheral retinal areas and for patients who previously could not be treated using the slit lamp method, such as children and mentally retarded patients. LIO can be used for therapy with argon, krypton, and diodes. Together with diodes, LIO is quite adequate, and now LIO

has replaced cryotherapy in cases of Retinopathy of Prematurity. Laser therapy can also use an endolaser probe during vitrectomy surgery. The probing used combines laser function and illumination capability even with aspiration capability.[5-8]

Indications and Complications of Laser Retinal Photocoagulation

Panretinal scatter used to destroy ischemic tissue to eliminate neovascularization in the retina, iris, and optic disc and to eliminate vascular proliferation in diabetic retinopathy and retinal vein occlusion. Focal ablation for nonelevated neovascularization in PDR and choroidal disease is also indicated in pan-retinal scatter. It is also indicated in masking intraretinal vascular abnormalities such as microaneurysms, telangiectasias, and perivascular leaks. In addition, chorioretinal attachment is where there is limited ablation and treatment for focal therapy in pigment epithelial disorders such as leakage associated with CSCR (Central Serous Chorio Retinopathy). In general, laser retinal photocoagulation is indicated for treating severe NPDR, PDR, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, retinal tears, lattice degeneration, subhyaloid bleeding, and central serous chorioretinopathy.[7,9]

Complications that can occur due to laser photocoagulation include foveal damage such as foveal burn, macular edema, epiretinal membrane/macular pucker, foveal spillover, and scarring. Other complications include choroidal hemorrhage, fibrous tissue contraction, visual function effects, and rare complications such as iris burns, choroidal effusion, and vitreous hemorrhage. To minimize complications, anticipation can usually be done by changing the laser parameters, namely power, duration, and spot size.[7,10]

Conclusion

Laser retinal photocoagulation is the standard therapy in diabetic retinopathy patients. However, this therapy can also be used for other retinal disorders. This laser beam works by causing thermal lesions in the pathological tissue, thus providing the desired outcome.

Conflict of Interest

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ORIGINAL ARTICLE **Open Access**

The Use of Digital Illustrators in Histology Practicum Learning of Medical Students In Gorontalo: Perception Study

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ABSTRACT

Introduction: Medical students need to learn histology to understand the relation between microscopic structure and function of cells and tissues. Pictures of manual preparation made by students can be used as notes and can describe students' understanding of the observed structures. Producing good pictures in a short time is a challenge for medical students. The use of digital illustrator technology is expected to be a solution to overcoming these problems. This study aims to measure the perception of acceptance and satisfaction rate of medical students in Gorontalo towards digital illustrators in apprehend histology practicum.
Method: Cross-sectional descriptive survey with modified questionnaires from previous studies. The sampling technique used purposive sampling and involved 54 first-year students. The raw data were analyzed using Microsoft Excel. The mean value calculated for each item was compared with the theoretical mean value of 2.50 to determine whether the respondents agreed with the statement.
Results: All items have an average rating exceeding the theoretical mean of 2.50. Also, the mean of 3.91 (SD = 0.58) for all items substantially exceeds the theoretical mean. Items with the highest perceived rate of perceived utility, ease of use, intention to use, and actual use of digital illustrator teaching materials in learning practical skills will significantly increase students' motivation, interest, and acquisition of practical skills.
Conclusion: the use of digital illustrators is perceived positively by medical students in helping histology practicum learning, which is indicated by the high rate of acceptance and rate of satisfaction with its use.

Key words: Digital illustrator, histology practicum, medical student

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Introduction

Histology studies the microscopic structure of normal cells and body tissues. This science is the basis for understanding disease pathology, diagnosis, and practice of medicine, as well as research in medicine and health.[1] Medical students need to study histology to understand the relationship between microscopic structure and function of cells and tissues. Studying histology requires observing two-dimensional images of tissues and organs, which are three-dimensional structures. The structure of the function of human tissue is a complex material because it is divided into sub-materials with a broad scope.

Drawings of manual preparation made by students can be used as notes and describe students' understanding of the observed structure. However, producing good pictures takes quite a long time, while in the medical curriculum, there is not much time allocation for practicum, so students tend to finish drawings without having time to observe the preparations seriously.[1] According to the Law of the Republic of Indonesia, number 20 of 2003, education is a conscious and planned effort to create a learning atmosphere and learning process so that students actively develop potential, personality, intelligence, noble character, and skills needed by themselves, in society, nation and state.[2] In education, the role of technology is an absolute value that must be mastered to meet the era of globalization with the competition of rapid technological advances. Online media, as a form of technological sophistication, plays a significant role in human life, improving health and education services for the world's citizens. In the digital era of benefits in the context of education, based on a study of the purpose of using technology in leading education in America, Alavi and Gallupe found several purposes of using technology, namely increasing competitive positioning, improving brand image, improving the quality of learning and teaching, increasing students' satisfaction, improve service quality, reduce operating costs, and develop new products and services.[3]

Digital illustrator aims to make it easier for medical students to understand the material and increase their understanding of medical histology. Therefore, this study aims to raise the acceptance and satisfaction rates of medical students in Gorontalo toward digital illustrators understanding histology practicum.

Methods

The study performed a cross-sectional descriptive survey with a modified questionnaire from a previous study.4 Rate of satisfaction and acceptance of digital illustrators (Biorender, Canada) were measured as the primary variable in this study. This

study was conducted at the Faculty of Medicine Universitas Negeri Gorontalo, Gorontalo, on March 2022. This study has complied with ethical clearance, and all participants gave their consent to participate in the study. Participation was based on their will, as presented in the first section of the questionnaire.

Population and Sample

The population was all 150 students studying at the Faculty of Medicine in the academic year 2021/2022. A first-year student who followed the biomedical subjects was included in this study. The student who had quit were excluded from this study. The study used purposive sampling and involved 54 first-year students, 11 men, and 43 women.

Data Collection Procedures

The data were collected in March 2022, in a single day. A google form was used for the study and distributed through social media groups. Therefore, it takes relatively little time for the respondents and researchers to complete and score the google form.

Method of Data Analysis

The raw data were analyzed using the Microsoft Excel 2010 version (Microsoft inc, USA). Initially, descriptive statistics such as percentages, means, and standard deviations were used to analyze the data collected. The computed mean rating for each item was compared with the theoretical mean rating (assuming a normal distribution of responses) of 2.50 to determine whether respondents agreed with the statements. Any computed mean of an item over 2.50 showed agreement with the statement, whereas item means less than 2.50 indicated disagreement.

Results

This study was conducted on 54 medical students with the frequency of gender, consisting of 11 men and 43 women. The level of acceptance and satisfaction of digital illustrators among students is shown in Table 1 and Table 2.

The computed mean rating for each item was compared with the theoretical mean rating (assuming a normal distribution of responses) of 2.50 to determine whether respondents agreed with the statements. Any computed mean of an item over 2.50 showed agreement with the statement, whereas item means less than 2.50 indicated disagreement with the statement. The results indicate that all the items had mean ratings far exceeding the theoretical mean of 2.50. All the items substantially exceeded the theoretical mean, they expressed high levels of perceived usefulness, ease of use, intention to use, and actual usage of the digital illustrator instructional materials in learning practical skills will significantly enhance learners' motivation, interest, and practical skills acquisition.

Table 1. Level of Acceptance of Digital Illustrator Among Medical Student

Element of acceptance of the digital illustrator	Mean Rating	Standard Deviation
Perceieved Usefullness		
1. Digital illustrator improve my performance in doing practical work in histology practice	4.06	0.76
2. Digital illustrator improve my acquisition of practical skills in histology practice preparate	4.13	0.82
3. Digital illustator enhance my effectiveness in performing practical work in	3.93	0.79
4. I find the Digital illustrator useful in acquiring practical skills in histology practice preparate	4.04	0.82
Perceived Ease of Use		
5. Operating the Digital illustrator is easy for me	3.85	0.80
6. I find it easy to get the Digital illustrator to learn practical lessons in histology practice preparate	3.89	0.83
7. It was easy for me to become skillful in learning practical lessons in histology practice preparate with the use of the Digital illustrator.	4.00	0.69
8. I find the Digital illustrator easy to use	3.81	0.86
Behavioural Intention to Use		
9. I intend to use the Digital illustrator regularly in learning practical lessons in histology practice preparate	3,70	0,96
Actual Usage		
10. l use the digital illustrator regularly to learn practical lessons in histology practice preparate	3,76	0,86

Table 2. Level of Satisfaction of Digital Illustrator Among Medical Student

Element of satisfaction with the digital illustrator	Mean Rating	Standard Deviation
1. I find the Digital illustrator lessons enjoyable.	3,81	0,86
2. The Digital illustrator have contributed greatly to my acquisition of relevant skills in histology practice preparate	3,94	0,78
3. I find the Digital illustrator lessons to be effective in meeting the learning objectives.	3,94	0,76

4. I would describe the Digital illustrator lessons as being highly interesting.	3,83	0,88
5. I would recommend use of the Digital illustrator lessons to my colleagues.	3,74	0,89
6. The Digital illustrator lessons make me spend more time studying to acquire practical skills.	3,80	0,89
7. I am satisfied with my learning from the Digital illustrator	3,93	0,84

Discussion

The acceptance level of students about the digital illustrator in their responses varies from "strongly agree" to "strongly disagree." Students' standard terms and phrases to express their satisfaction with the digital illustrator include strongly disagree, disagree, neutral, agree, and strongly agree. The mean rating for each of the ten learner acceptance items as rated by the respondents and the resultant mean rating for all the items were computed and compared with the theoretical mean rating (assuming a normal distribution of responses) of 2.50. This reference was to determine whether students responded positively to the digital illustrator. The computed means and the corresponding standard deviations appear in Table 1. Table 1 indicates that all the items had mean ratings far exceeding the theoretical mean of 2.50. Also, the mean of 3,91 (*SD* = 0.58) for all the items substantially exceeded the theoretical mean. As indicated in Table 1, the item "I intend to use the Digital illustrator regularly in learning practical lessons in histology practice preparate" (Item #9) had the least mean rating of 3.70 (*SD* = 0.96). Though it had the least mean rating, the value of 3.310 substantially exceeded the theoretical mean of 2.50. The highest mean rating of 4.13 (*SD* = 0.82) related to the item "Digital illustrator improve my acquisition of practical skills in histology practice preparate" (Item #2). The reported high ease of use could be due to the quality of the materials regarding content, text, images, and sound. Indeed, when viewed, the images appear suitable and visible; the texts are visible and easy to read, as the fonts are bold and precise; there is a good contrast with the background, and the screens appear clean and uncluttered. Thus, the study's results showed that distant learners responded positively to the digital illustrator and that the materials were well received. It is hoped that the expressed high levels of perceived usefulness, ease of use, intention to use, and actual usage of the digital illustrator instructional materials in learning practical skills will significantly enhance learners' motivation, interest, and practical skills acquisition.

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The satisfaction level of students about the digital illustrator in their responses varies from "strongly agree" to "strongly disagree." Students' common terms and phrases to express their satisfaction with the digital illustrator include strongly disagree, disagree, neutral, agree, and strongly agree. Most of the respondents indicated that they were satisfied with the digital illustrator. "The digital illustrator has contributed greatly to my acquisition of relevant skills in histology practice preparate" and "I find the Digital illustrator lessons to be effective in meeting the learning objectives." The mean rating for each of the ten learner acceptance items as rated by the respondents was computed for each of the three study centres that participated in the study (Table 2). The mean ratings for the three sub-groups are high and appear quite close for many items. The result notwithstanding, it was deemed appropriate to determine whether the observed differences were statistically significant, using a digital illustrator at the 0.05 level of significance.

Attitudes Towards Using (ATU), Behavioural Intention (BI), and Actual Usage (AU) are defined as follows: Perceived Usefulness (PU) is defined as the degree to which a person believes that using an IT system would improve his/her job performance.[5] Perceived Ease of Use (PEOU) is the degree to which a person believes using an information technology would be free of effort. Attitudes Towards Using (ATU) is a function of beliefs, positively or unfavorably, towards the behavior. Behavioral Intention (BI) is our goals, aspirations, and expected responses to the attitude object. Actual Usage (AU) is defined as the frequency of using a new technology system, such as mobile voting, and the approximate number of times the user uses it in a given period.

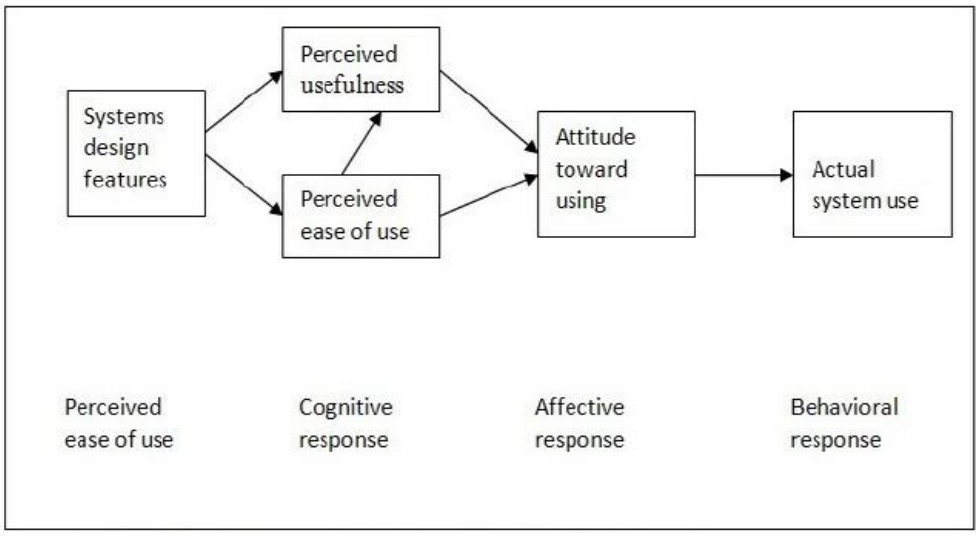

Figure 1. Original Technology Acceptance Model (TAM).[5]

"Engagement and Technology Integration Theory" developed by Gunuc was used within the scope of the research. In this theory, technology integration is discussed at the micro level. In-class and out-of-class teaching and learning activities have been designed. The basis of this theory is not only the teacher. Both the teacher and the student are at the center. The basic idea of the theory is to explain that student engagement and technology integration are related to student success and practical learning. Gunuc expresses student engagement as follows: "Student engagement is the quality and quantity of the student's psychological, cognitive, affective, behavioral responses and energies to participate in the learning process, academic and social activities inside/outside the classroom to achieve successful learning outcomes."

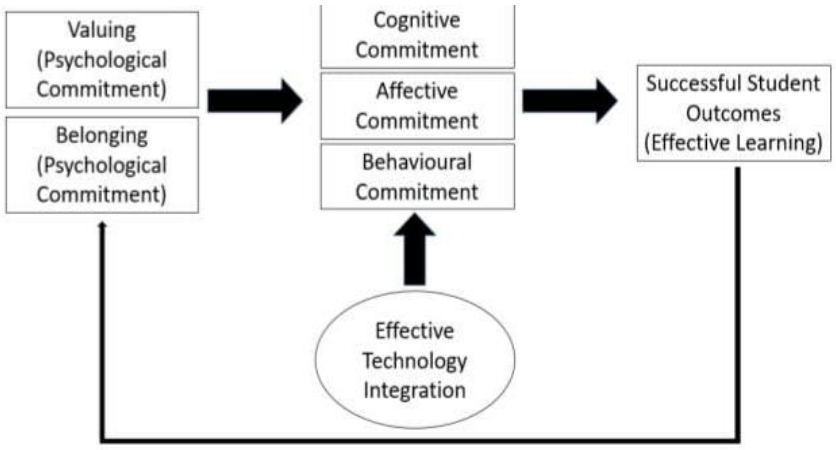

Figure 2. The Engagement and Technology Integration Theory.[6]

When the previous theory is examined, first of all, it is necessary to emphasize students' feelings of value and belonging. After these steps are fulfilled, activities should be done to create cognitive, affective, and behavioral commitment. These should be accomplished by providing practical technology integration. As a result, feelings of commitment will be combined with technology integration, and effective learning outcomes will be created.

Conclusion

Based on the research results that have been done, it is concluded that there showed high acceptance and satisfaction of the digital illustrator in practical skills. The learners expressed high perceived usefulness, ease of use, and intention to use the digital illustrator in learning practical histology skills. The learners also found the materials relevant, effective, enjoyable, and exciting and would recommend them to their fellow students for use. The

expressed high acceptance of and satisfaction with the video-based instructional materials was, to a large extent, also uniform among the respondents of the three study centers. Thus, irrespective of location, the learners generally appeared optimistic about their experiences using the digital illustrator to learn histology practicals in medical faculty.

Conflicts of Interest

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