JYMS
JOURNAL OF YEUNGNAM
MEDICAL SCIENCE

JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Vol. 39 No. 2 April 2022

JYMS
JOURNAL OF YEUNGNAM
MEDICAL SCIENCE

eISSN 2799-8010

Vol. 39 No. 2
April 2022

Vol. 39 No. 2 April 2022

page 81-177

YEUNGNAM UNIVERSITY
COLLEGE OF MEDICINE

YEUNGNAM UNIVERSITY
INSTITUTE MEDICAL SCIENCE

www.e-jyms.org

e-jyms.org
eISSN 2799-8010

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Vol. 39 • No. 2 • April 2022

Aims and scope

Journal of Yeungnam Medical Science (J Yeungnam Med Sci, JYMS, eISSN 2799-8010, https://e-jyms.org), the official publication of the Yeungnam University College of Medicine and Yeungnam University Institute Medical Science, is a peer-reviewed and open access journal in the medical field. Its regional focus is mainly Korea, but it welcomes submissions from researchers all over the world.

JYMS aims to communicate new medical information to medical personnel, and to facilitate the development of medicine and the propagation of medical knowledge by publishing high quality evidence-based articles. It covers all fields of medical science, including clinical research and basic medical science.

JYMS publishes editorials, review articles, original articles, case reports, image vignettes, communications, and imagery. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and for the communication of valuable information about all fields of medicine.

The first volume was published in December 1984 in Korean. YUJM is being published in English since 2018 and Journal title changed from YUJM to JYMS in January 2022. JYMS is published in English, four times a year (January 31, April 30, July 31, and October 31).

JYMS is indexed/tracked/covered by PubMed Central, PubMed, CAS, DOAJ, KoreaMed, Korea Citation Index, KoMCI, WPRIM, DOI/CrossRef, and Google Scholar.

Open access

Publisher
Yeungnam University College of Medicine, Yeungnam University Institute of Medical Science

Editor-in-chief
So-Young Park, Yeungnam University College of Medicine

Editorial office
Yeungnam University College of Medicine
170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6832 • Fax: +82-53-651-0394 • E-mail: jyms@yu.ac.kr

Printing office
M2PI
8th FL, DreamTower, 66 Seongsui-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-6966-4930 • Fax: +82-2-6966-4945 • E-mail: support@m2-pi.com

Published on April 30, 2022

Editorial board

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

eISSN 2799-8010

Contents

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Vol. 39 · No. 2 · April 2022

Imagery

Review articles

Original articles

eISSN 2799-8010

Contents

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Vol. 39 · No. 2 · April 2022

Case reports

Imagery

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):i
https://doi.org/10.12701/jyms.2022.00136

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

"Another color of the world"

Laugavegur trail in Iceland

Photograph by In Hwan Song, Daegu, Korea

The "Imagery" section of Journal of Yeungnam Medical Science (JYMS) is devoted to the artistic and imaginative qualities of our readers. JYMS invites you to submit your drawings, illustrations, or photographs, along with appropriate explanatory information, for publication within this section. Please forward electronic images via e-mail to: jyms@yu.ac.kr.

Review article

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):81-88
https://doi.org/10.12701/yujm.2021.01228

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Current diagnosis and treatment of vestibular neuritis: a narrative review

Chang Hoon Bae, Hyung Gyun Na, Yoon Seok Choi

Department of Otorhinolaryngology-Head and Neck Surgery, Yeungnam University College of Medicine, Daegu, Korea

Vertigo is the sensation of self-motion of the head or body when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement. Representative peripheral vertigo disorders include benign paroxysmal positional vertigo, Ménière disease, and vestibular neuritis. Vestibular neuritis, also known as vestibular neuronitis, is the third most common peripheral vestibular disorder after benign paroxysmal positional vertigo and Ménière disease. The cause of vestibular neuritis remains unclear. However, a viral infection of the vestibular nerve or ischemia of the anterior vestibular artery is known to cause vestibular neuritis. In addition, recent studies on immune-mediated mechanisms as the cause of vestibular neuritis have been reported. The characteristic clinical features of vestibular neuritis are abrupt true-whirling vertigo lasting for more than 24 hours, and no presence of cochlear symptoms and other neurological symptoms and signs. To accurately diagnose vestibular neuritis, various diagnostic tests such as the head impulse test, bithermal caloric test, and vestibular-evoked myogenic potential test are conducted. Various treatments for vestibular neuritis have been reported, which are largely divided into symptomatic therapy, specific drug therapy, and vestibular rehabilitation therapy. Symptomatic therapies include generalized supportive care and administration of vestibular suppressants and antiemetics. Specific drug therapies include steroid therapy, antiviral therapy, and vasodilator therapy. Vestibular rehabilitation therapies include generalized vestibular and customized vestibular exercises.

Keywords: Diagnosis; Treatment; Vertigo; Vestibular neuritis

Introduction

Vertigo is the sensation of self-motion of the head or body when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement [1]. The occurrence of vertigo can be divided into peripheral disorders that originate in the vestibular organs and central disorders that originate in the brain. Representative peripheral vertigo disorders include benign paroxysmal positional vertigo, Ménière disease, and vestibular neuritis.

Benign paroxysmal positional vertigo is one of the most prevalent vestibular disorders and is characterized by recurrent positional vertigo without hearing loss [2]. According to a widely accepted theory, benign paroxysmal positional vertigo is usually caused by otoconia that are dislodged from the otolith macula beds and are trapped in the semicircular canal. The otoconia move under the influence of gravity after changes in head position in the plane of the affected semicircular canal; the resulting inappropriate endolymph flow deflects the cupula and thus modulates the activity of the vestibular afferents of the affected canal, causing attacks of positional vertigo and nystagmus (canalolithiasis) [3]. The definitive diagnosis of benign paroxysmal positional vertigo requires diagnostic po-

Received: June 14, 2021 • **Revised:** July 16, 2021 • **Accepted:** July 22, 2021
Corresponding author: Chang Hoon Bae, MD, PhD
Department of Otorhinolaryngology-Head and Neck Surgery, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3784 • Fax: +82-53-628-7884 • E-mail: baich@med.yu.ac.kr

sitional maneuvers that involve the provocation of vertigo and nystagmus in each semicircular canal, and the effective treatment of benign paroxysmal positional vertigo includes therapeutic positional maneuvers such as the Epley, Semont, and Gufoni maneuvers [2,3].

Ménière disease is characterized by recurrent spontaneous vertigo, fluctuating hearing loss, tinnitus, and aural fullness. The pathophysiological findings of Ménière disease are associated with an accumulation of endolymph in the cochlear duct, which occurs at the expense of the perilymphatic space, and inadequate absorption of the endolymph by the endolymphatic sac [2,4]. The diagnosis of Ménière disease is based on the 2015 clinical criteria proposed by the International Classification Committee for Vestibular Disorders of the Bárány Society [5]. Ménière disease is treated with dietary modification; administration of betahistine, diuretics, intratympanic steroids, and intratympanic gentamicin; endolymphatic sac surgery, labyrinthectomy, and vestibular neurectomy [2].

Vestibular neuritis is characterized by acute spontaneous vertigo without hearing loss and is the third most common peripheral vestibular disorder, after benign paroxysmal positional vertigo and Ménière disease [2]. Vestibular neuritis is classified as an acute vestibular syndrome, like vestibular migraine, multiple sclerosis, and stroke [1]. Although vestibular neuritis is considered to be triggered by viral inflammation or reactivation of latent viruses in the ganglion of the vestibular nerve [2,6], the exact etiology of vestibular neuritis is not yet clear. Therefore, various treatments have been used for vestibular neuritis, such as corticosteroids, antivirals, and vestibular rehabilitation exercises [6]. This study aimed to review the etiology, epidemiology, diagnosis, and treatment of vestibular neuritis, focusing on the current diagnosis and treatment of vestibular neuritis.

Terminology

Vestibular neuritis is an acute peripheral vestibulopathy, also known as vestibular neuronitis. The clinical features of vestibular neuritis were first reported by Eric Ruttin in 1909 and later by Carl-Olof Nylén in 1924 [7,8]. The term "vestibular neuronitis" was first described by Charles Skinner Hallpike in 1949 and Margret Ruth Dix and Charles Skinner Hallpike in 1952 [9]. Vestibular neuronitis was replaced by the term "vestibular neuritis," because there is strong evidence that the vestibular ganglion cells themselves are not inflamed, but rather parts of the vestibular nerve [7]. Recently, it has been recommended to consider vestibular neuritis as an acute unilateral vestibulopathy according to the International Classification of Vestibular Disorders [10].

Epidemiology

Peripheral vertigo is most common in benign paroxysmal positional vertigo, followed by Ménière disease, and vestibular neuritis [2,10]. The annual incidence of vestibular neuritis has been reported to range from 3.5% to 15.5% per 100,000 persons [10-13], and approximately 4% to 9.8% of adult patients and 3.3% of pediatric patients are treated for acute unilateral vestibular loss [14]. Although vestibular neuritis has been reported to occur more frequently in women than in men, there is no statistically significant difference in the incidence between men and women [11,15]. Vestibular neuritis occurs mainly in patients aged 30 to 60 years and most often occurs in those aged 40 to 50 years. According to a recent study, vestibular neuritis has been reported to occur even more frequently in those over the age of 70 years [10,15].

Etiology

The exact etiology of vestibular neuritis remains unclear. However, viral infection of the vestibular nerve or ischemia of the anterior vestibular artery is thought to cause vestibular neuritis. In addition, recent studies on immune-mediated mechanisms as the cause of vestibular neuritis have been reported [16-18].

Regarding viral infection of the vestibular nerve, it is considered that viruses causing infections of the upper respiratory tract, such as influenza virus, adenovirus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and parainfluenza virus are related to vestibular neuritis, because associations with preceding or concurrent viral infection in the upper respiratory tract occur in 43% to 46% of vestibular neuritis [16]. Among them, herpes simplex virus type 1 is the most common cause of viral infection of the vestibular nerve and ganglion; the deoxyribonucleic acid of herpes simplex virus type 1 is detected on autopsy in about two of three human vestibular ganglia along with the expression of CD8-positive T lymphocytes, cytokines, and chemokines [17], and inoculation of herpes simplex virus type 1 into a mouse model induces vestibular dysfunction in infected vestibular ganglion cells, such as vestibular neuritis [17,18].

As a result of ischemia of the anterior vestibular artery, the inflammatory response of peripheral blood mononuclear cells and the percentage of CD40-positive monocytes and macrophages are significantly elevated in patients with vestibular neuritis compared to healthy individuals [16]. The pro-inflammatory activation of peripheral blood mononuclear cells, CD40-positive monocytes, CD40-positive macrophages, and cytokines such as tumor necrosis factor alpha, cellular adhesion molecule, and cyclooxygenase 2, leads to reduced microvascular perfusion of the vestibular organ

 https://doi.org/10.12701/yujm.2021.01228

caused by an increase in thrombotic events, which causes a loss of function of the vestibular organ secondary to reduced perfusion and/or infarction [16,18].

Vestibular neuritis occurs mainly in the superior vestibular nerve, which innervates the anterior semicircular canal, lateral semicircular canal, and utricle, rather than the inferior vestibular nerve [10,16,17]. Swelling due to viral infection or ischemia mainly occurs in the superior vestibular verve because of anatomical differences between the superior and inferior vestibular nerves; the bony canal of the superior vestibular nerve and arteriole is a relatively narrower passage and seven times longer than the bony canal of the singular nerve [10,17].

Regarding immune-mediated mechanisms, an immunological imbalance between T-helper and T-suppressor cells is associated with vestibular neuritis, similar to that observed in multiple sclerosis [16,18].

Diagnosis

The characteristic clinical features of vestibular neuritis are abrupt true-whirling vertigo lasting for more than 24 hours with nausea and vomiting in middle age, and no presence of cochlear symptoms and other neurological symptoms and signs, such as hearing loss, tinnitus, stuttering, and paresthesia of the ipsilateral face and contralateral upper and lower extremities. Prodromal dizziness lasting a few minutes, in the few days just before the full onset of symptoms, may precede the prolonged spontaneous vertigo in as many as a quarter of patients with vestibular neuritis, who mostly experience non-vertiginous dizziness attacks, often accompanied by nausea or unsteadiness, which may develop abruptly or gradually [19]. The vertigo of vestibular neuritis increases gradually over several hours, peaking on the first day. It is usually described as rotational and is significantly increased by head movements. Patients with vestibular neuritis usually prefer lying down in bed with their eyes closed in a side position with the healthy ear down. Most vertiginous patients experience severe nausea and vomiting, which improve significantly over a period of 1 to 3 days [17,19].

Patients with vestibular neuritis can walk alone in the acute stage, usually the first 3 days after the onset of symptoms, but most are supported by a caregiver because the body tilts toward the lesioned side or tends to fall. During the acute stage of vestibular neuritis, horizontal-torsional spontaneous nystagmus beating away from the lesioned side is observed, which is of a unidirectional type and obeys Alexander's law: the horizontal nystagmus typically increases during gaze in the direction of the quick phases and decreases when looking in the opposite direction [17,19,20]. In addition, the ocular tilt reaction comprises head tilt, ocular torsion, and skew deviation. However, the full picture of the ocular tilt reaction is not very often seen clinically [21]. In the recovery stage of vestibular neuritis, the horizontal-torsional spontaneous nystagmus beating toward the lesioned side is observed [17,19,20].

The head impulse test is a simple bedside test of the higher frequency vestibulo-ocular reflex, which is based on Ewald's second law. It is performed by grasping the patient's head and applying a brief, small-amplitude, high-acceleration head turn, first to one side and then to the other. The patient fixates on the examiner's nose, and the examiner watches for corrective rapid movement of the eye (saccades), which is a sign of decreased vestibular response. The "catch-up" saccades after a head impulse in one direction indicate a peripheral vestibular lesion on that side [22]. The bedside head impulse test has an acceptable sensitivity, but may appear negative when the vestibular deficits are mild or the corrective saccades that only occur during head impulses and cannot be seen on simple visual inspection. In these instances, a video head impulse test is necessary; the findings of the video head impulse test in vestibular neuritis show decreased gain and corrective overt and covert saccades [19,22,23].

Head shaking nystagmus is generated by an asymmetric peripheral vestibular input and a central velocity storage mechanism, which may cause perseveration of the peripheral vestibular signals, with the subsequent reversal phase indicating adaptation of primary vestibular afferent activity [24]. The head-shaking nystagmus test is performed by rotating the patient's head vigorously 20 times at 2 Hertz with the patient's head inclined at 30° while sitting. The findings of head-shaking nystagmus test in vestibular neuritis show monophasic or biphasic type: the monophasic type is characterized by a slow-phase component toward the lesioned side, and the biphasic type is characterized by an initial slow-phase component toward the lesioned side, followed by a prolonged reversal phase toward the opposite side [24,25].

The smooth pursuit test measures the slow movement of the eye to stabilize the image of an object on or near the fovea for optimal visual acuity during the slow movement of the object or body, while the optokinetic nystagmus test measures rapid eye movement in the physiological response induced by a series of displays moving rapidly across the visual field [26,27]. The findings of the smooth pursuit test and optokinetic test in vestibular neuritis show abnormal findings, such as corrective catch-up saccades, decreased gain, and asymmetry, which must be used to differentiate between vestibular neuritis and central nervous system disease [28].

The subjective visual vertical/horizontal test measures otolith dysfunction without complex equipment: the ipsilesional deviation of the subjective visual vertical and horizontal senses [29]. The findings of the subjective visual vertical/horizontal test show a

significant deviation of the tilting bar at least 2.5° toward the lesioned side [17,29].

The caloric test involves stimulation of the horizontal semicircular canal by alternating heating and cooling of the external auditory canal with water or air. Although the caloric test can only evaluate the function of the horizontal semicircular canal in the lower frequency range of stimulation, the bithermal caloric test provides the most characteristic and consistent results in vestibular neuritis. The findings of the caloric test show more than 20% to 30% of canal paresis on the affected side and directional preponderance on the healthy side in superior vestibular neuritis, but normal results in inferior vestibular neuritis (Fig. 1A) [17,30] .

Vestibular-evoked myogenic potentials are short-latency, vestibular-dependent reflexes that are recorded from the sternocleidomastoid muscles in the anterior neck (cervical vestibular-evoked myogenic potentials) and inferior oblique extraocular muscles (ocular vestibular-evoked myogenic potentials). They are evoked by short bursts of sound delivered through headphones or vibrations applied to the skull. These stimuli have been shown to preferentially activate the saccule and utricle [31]. The findings of vestibular-evoked myogenic potential tests in vestibular neuritis show decreased or absent responses of vestibular-evoked myogenic potentials during stimulation of the affected ear [17]. Furthermore, the dissociated patterns of abnormalities in cervical and ocular vestibular-evoked myogenic potentials may provide important clues for determining the involved vestibular division in vestibular neuritis: abnormal ocular vestibular-evoked myogenic potentials but normal cervical vestibular-evoked myogenic potentials in response to air-conducted sound in superior vestibular neuritis, whereas normal ocular vestibular-evoked myogenic potentials but abnormal cervical vestibular-evoked myogenic potentials in response to air-conducted sound are seen in inferior vestibular neuritis [17,31].

Posturography is used to quantify the relative contributions of

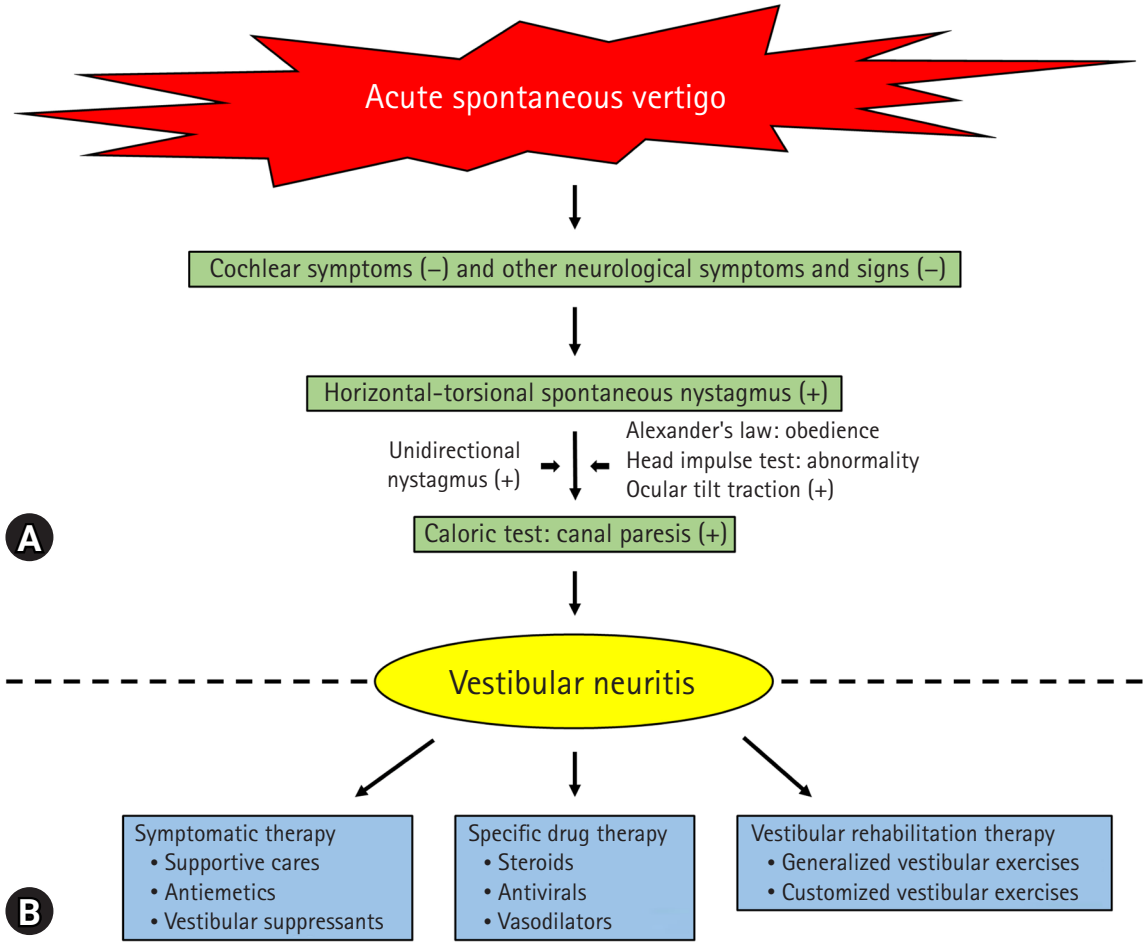

Fig. 1. Diagnostic evaluation and treatment of vestibular neuritis. (A) Characteristic clinical features of vestibular neuritis include acute spontaneous vertigo and no presence of cochlear symptoms and other neurological symptoms and signs. Horizontal-torsional spontaneous nystagmus is observed with canal paresis on the affected side. (B) Various treatments of vestibular neuritis include symptomatic therapy, specific drug therapy, and vestibular rehabilitation therapy. –, negative; +, positive.

 https://doi.org/10.12701/yujm.2021.01228

sensory systems to postural control in the upright stance under either static or dynamic conditions, and can provide insight into the presence of postural instability and help identify which sensory system is involved, although it does not provide a topographic diagnosis [32]. The findings of computerized dynamic posturography in vestibular neuritis show abnormal results for conditions 5 and/or 6 of the sensory organization test [32,33].

In contrast to the caloric test, the rotational test provides physiological stimuli and quantitative evaluation of the vestibulo-ocular reflex function of the horizontal semicircular canals, and expands the ability to investigate the peripheral vestibular system beyond the very low-frequency region [34]. The findings of the rotational chair test show decreased gain, asymmetry, and phase lead in the sinusoidal harmonic acceleration test, and a decreased time constant in the step-velocity test [34,35].

Magnetic resonance imaging is usually performed to distinguish lesions of the central nervous system in acute vestibular syndromes, such as vestibular migraine, multiple sclerosis, and stroke. Gadolinium-enhanced 3 T magnetic resonance imaging in vestibular neuritis allows direct visualization of the affected vestibular nerve [17,36].

Diseases that should be distinguished from vestibular neuritis include vestibular migraine, benign paroxysmal positional vertigo, Ménière disease, multiple sclerosis, stroke, and transient ischemic attack. A definite diagnosis of benign paroxysmal positional vertigo requires diagnostic positional maneuvers that involve the provocation of vertigo and nystagmus in each semicircular canal. To diagnose posterior or anterior semicircular canal benign paroxysmal positional vertigo, the Dix-Hallpike maneuver is conducted by turning the head of a sitting patient 45° toward the side to be tested and then laid back quickly into a head-hanging position; the side-lying maneuver is conducted so that the sitting patient is tilted quickly to the side to be tested with the head turned 45° to the opposite side [2,3]. To diagnose horizontal semicircular canal benign paroxysmal positional vertigo, the head roll test is conducted in which the head of the patient in the supine position is elevated by about 30° and then turned quickly to either side [3]. The diagnosis of Ménière disease is based on the 2015 clinical criteria proposed by the International Classification Committee for Vestibular Disorders of the Bárány Society: (1) two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours; (2) audiometrically documented low- to medium-frequency sensorineural hearing loss in the affected ear on at least one occasion before, during, or after one of the episodes of vertigo; (3) fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear; and (4) not better accounted for by another vestibular diagnosis [2,4,5]. In stroke, central nystagmus is pure vertical nystagmus or rotational nystagmus. The direction of the nystagmus also changes according to the direction of the gaze; fixation has little to no effect. In addition, it is often difficult to walk or stand due to severe body sway. It may be accompanied by central nervous system-related symptoms, such as stuttering and paresthesia of the ipsilateral face and contralateral upper and lower extremities [17]. Vestibular pseudoneuritis caused by an isolated infarction of the labyrinthine, pontomedullary brainstem, or cerebellum requires a more meticulous differential diagnosis [1,19]. It is not always easy to distinguish between isolated vascular vertigo and acute peripheral vestibulopathy at the bedside. However, a rather simple neuro-otological examination, including a normal horizontal head impulse test, direction-changing nystagmus, and skew deviation can reliably detect central vertigo with high sensitivity and specificity. Even these neuro-otological examinations are more sensitive to stroke than early magnetic resonance imaging [17].

Treatment

Various treatments for vestibular neuritis have been reported, which can be largely divided into symptomatic therapy, specific drug therapy, and vestibular rehabilitation therapy (Fig. 1B). Symptomatic therapy reduces anxiety by explaining in detail the cause, treatment, and prognosis of vestibular neuritis in patients, and provides psychological support by explaining that daily life is possible in a short period of time. It also ensures that the patient is in the most comfortable position and that secondary damage from falls does not occur. In the acute stage of vestibular neuritis, nausea and vomiting are common. Therefore, if food intake is difficult, appropriate fluid therapy is needed, and vestibular suppressants and antiemetics should be administered [19,37].

Vestibular suppressants are widely used because they are effective against dizziness, nausea, and vomiting. Although the exact mechanism of action of vestibular suppressants is unclear, they act at the level of the neurotransmitters involved in the propagation of impulses from primary to secondary vestibular neurons and in the maintenance of tone in the vestibular nuclei. They also act on areas of the nervous system that control vomiting, including central components in the emetic center of the brain and peripheral components in the gastrointestinal tract [38]. Representative vestibular suppressants include antihistamines such as dimenhydrinate and meclizine; anticholinergics such as scopolamine and atropine; antidopaminergics such as haloperidol and droperidol; γ-aminobutyric acid receptor agonists such as diazepam, lorazepam, and clonazepam, and calcium channel blockers such as flunarizine. Representative antiemetics include antidopaminergics such as domperidone and metoclopramide, and serotonin receptor antag-

onists, such as ondansetron [17,18]. During the acute stage of vestibular neuritis, an intramuscular or intravenous route for vestibular suppressants and antiemetics is usually preferable because of severe nausea and decreased gastric motility. The response is clearly dose-dependent; therefore, if the initial dose is not effective, higher doses should be administered [38]. However, most vestibular suppressants can have sedative effects, so they should not be used when patients are engaged in activities that require a high level of alertness, such as driving, operating machinery, or participating in athletic activities; long-term use of vestibular suppressants, which should be used carefully while monitoring the patient's recovery progress, is known to delay the central compensation of vestibular neuritis [19,38].

Regarding specific drug therapy, steroid therapy has been reported to relieve dizziness and promote vestibular compensation in vestibular neuritis; methylprednisolone is much more effective than placebo in reducing vertiginous symptoms in patients with acute vestibular vertigo [39], and early treatment of acute vestibular neuritis with high doses of glucocorticoids accelerates and improves the recovery of vestibular function [40]. However, some reports have shown that steroid therapy has no beneficial effects on the long-term prognosis of vestibular neuritis [41,42]. Therefore, steroid therapy for vestibular neuritis has yet to be clarified and is provided on an individual basis [18,40]. Antiviral therapy based on the etiology of viral infection of vestibular neuritis has also been reported. However, administration of antivirals alone or in combination with steroids has no therapeutic effect on vestibular neuritis [17,43]. In addition, vasodilator therapy based on the etiology of ischemia of vestibular neuritis has not yet been proven to have a therapeutic effect in vestibular neuritis [44].

In vestibular rehabilitation therapy, the goals are to improve vertigo, gaze stability, postural stability, and daily living activities through vestibular compensation and central neuroplasticity [45,46]. Vestibular compensation can be divided into static and dynamic compensation [47]. Static compensation is usually attributed to the restoration of symmetry in the resting discharge rates of secondary neurons on the two sides of the brainstem. The rebalancing of resting discharges in the vestibular nuclei may involve a decrease in the efficacy of both γ-aminobutyric acid type A and type B receptors and an increase in neuronal excitability on the damaged side [47,48]. Dynamic compensation refers to the compensation of vestibular reflexes that are activated by movement and is composed of adaptation, habituation, and substitution [17,45,47,49]. It is achieved through vestibular rehabilitation exercises that are safe, highly therapeutic, and highly cost-effective for patients with vestibular neuritis [49-51].

Vestibular rehabilitation exercises are mainly divided into generalized and customized vestibular exercises. A representative generalized vestibular exercise is the Cawthorne-Cooksey exercise, and representative customized vestibular exercises include adaptation exercises, habituation exercises, balance and gait exercises, and general conditioning exercises, which are more effective than generalized vestibular exercises [46,52]. Vestibular exercises significantly hasten vestibulospinal compensation in patients with acute vestibular neuritis [17]. Balance and gait exercises significantly reduce the time required for vestibulospinal compensation [19]. Voluntary eye movements, active head movements, goal-directed movements, and walking should be encouraged to restore postural control and balance as soon as possible. Patients with vestibular neuritis should exercise for at least 30 minutes three times a day [17,19].

Regarding the prognosis, most patients with vestibular neuritis have subacute or acute spontaneous vertigo that gradually aggravates over several hours and reaches a peak within the first day. Severe vertigo improves markedly within a day or two, with residual symptoms gradually resolving over the following weeks [17]. The symptoms and signs of static vestibular imbalances, such as spontaneous nystagmus, ocular torsion, and ipsilesional subjective visual vertical tilt, are mostly resolved by 3 months after the onset of vestibular neuritis, while the signs of dynamic vestibular imbalances, such as corrective saccades of head impulse test, head shaking nystagmus, vibration-induced nystagmus, and caloric paresis, persist over 1 year in more than 30% of patients with vestibular neuritis [19]. The persistent imbalance that some patients experience after acute vestibular neuritis may be due to many factors, including inadequate central compensation, incomplete peripheral recovery, and psychophysiological and psychological features. Vestibular neuritis is known to recur in only 2% to 11% of cases [17,19].

Conclusion

Vestibular neuritis, also known as vestibular neuronitis, is a representative peripheral vertigo. The causes of vestibular neuritis are not yet clear, but mainly viral infection, ischemia, and immune-mediated mechanisms. The characteristic clinical features of vestibular neuritis are abrupt true-whirling vertigo lasting for more than 24 hours, and no presence of cochlear symptoms and other neurological symptoms and signs. To accurately diagnose vestibular neuritis, various diagnostic tests such as the head impulse test, bithermal caloric test, and vestibular-evoked myogenic potential test are conducted. Symptomatic therapy, specific drug therapy, and vestibular rehabilitation therapy have been studied and implemented for the treatment of vestibular neuritis. Nevertheless, additional studies are needed to clarify the cause, diagnosis, and treatment of vestibular neuritis in the future, and this review is expected to pro-

 https://doi.org/10.12701/yujm.2021.01228

vide more information on the diagnosis and treatment of patients with acute spontaneous vertigo.

Notes

Conflicts of interest

No potential conflicts of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization: CHB, HGN, YSC; Formal analysis, Supervision: CHB, HGN; Writing - original draft: CHB; Writing - review & editing: CHB, YSC.

ORCID

Chang Hoon Bae, https://orcid.org/0000-0002-0835-4060
Hyung Gyun Na, https://orcid.org/0000-0003-4017-4796
Yoon Seok Choi, https://orcid.org/0000-0002-0616-7122

References

1. Bisdorff AR, Staab JP, Newman-Toker DE. Overview of the International Classification of Vestibular Disorders. Neurol Clin 2015;33:541–50.
2. Strupp M, Mandalà M, López-Escámez JA. Peripheral vestibular disorders: an update. Curr Opin Neurol 2019;32:165–73.
3. von Brevern M, Bertholon P, Brandt T, Fife T, Imai T, Nuti D, et al. Benign paroxysmal positional vertigo: diagnostic criteria. J Vestib Res 2015;25:105–17.
4. Tabet P, Saliba I. Meniere's disease and vestibular migraine: updates and review of the literature. J Clin Med Res 2017;9:733–44.
5. Lopez-Escamez JA, Carey J, Chung WH, Goebel JA, Magnusson M, Mandalà M, et al. Diagnostic criteria for Menière's disease. J Vestib Res 2015;25:1–7.
6. Whitman GT. Dizziness. Am J Med 2018;131:1431–7.
7. Brandt T. Vestibular neuritis. In: Brandt T. Vertigo: its multisensory syndrome. 2nd ed. London: Springer-Verlag; 2003. p. 67–81.
8. Nylén CO. Some cases of ocular nystagmus due to certain positions of the head. Acta Otolaryngol (Stockholm) 1924;6:106–37.
9. Lumio JS, Aho J. Vestibular neuronitis. Ann Otol Rhinol Laryngol 1965;74:264–70.
10. Strupp M, Magnusson M. Acute unilateral vestibulopathy. Neurol Clin 2015;33:669–85.
11. Adamec I, Krbot Skorić M, Handžić J, Habek M. Incidence, seasonality and comorbidity in vestibular neuritis. Neurol Sci 2015;36:91–5.
12. Strupp M, Brandt T. Vestibular neuritis. In: Bronstein AM, editor. Oxford textbook of vertigo and imbalance. Oxford: Oxford University Press; 2013. p. 207–16.
13. Neuhauser HK. Epidemiology of vertigo. Curr Opin Neurol 2007;20:40–6.
14. Wiener-Vacher SR, Quarez J, Priol AL. Epidemiology of vestibular impairments in a pediatric population. Semin Hear 2018;39:229–42.
15. Hülse R, Biesdorf A, Hörmann K, Stuck B, Erhart M, Hülse M, et al. Peripheral vestibular disorders: an epidemiologic survey in 70 million individuals. Otol Neurotol 2019;40:88–95.
16. Greco A, Macri GF, Gallo A, Fusconi M, De Virgilio A, Pagliuca G, et al. Is vestibular neuritis an immune related vestibular neuropathy inducing vertigo? J Immunol Res 2014;2014:459048.
17. Jeong SH, Kim HJ, Kim JS. Vestibular neuritis. Semin Neurol 2013;33:185–94.
18. Le TN, Westerberg BD, Lea J. Vestibular neuritis: recent advances in etiology, diagnostic evaluation, and treatment. Adv Otorhinolaryngol 2019;82:87–92.
19. Kim JS. When the room is spinning: experience of vestibular neuritis by a neurotologist. Front Neurol 2020;11:157.
20. Shikino K, Ikusaka M. Alexander's law in vestibular neuritis. BMJ Case Rep 2021;14:e239705.
21. Halmagyi GM, Gresty MA, Gibson WP. Ocular tilt reaction with peripheral vestibular lesion. Ann Neurol 1979;6:80–3.
22. Choi KD, Oh SY, Kim JS. Head thrust test. Ann Clin Neurophysiol 2006;8:1–5.
23. Kattah JC. Use of HINTS in the acute vestibular syndrome. An overview. Stroke Vasc Neurol 2018;3:190–6.
24. Lee YJ, Shin JE, Park MS, Kim JM, Na BR, Kim CH, et al. Comprehensive analysis of head-shaking nystagmus in patients with vestibular neuritis. Audiol Neurootol 2012;17:228–34.
25. Hain TC, Fetter M, Zee DS. Head-shaking nystagmus in patients with unilateral peripheral vestibular lesions. Am J Otolaryngol 1987;8:36–47.
26. Sharpe JA. Neurophysiology and neuroanatomy of smooth pursuit: lesion studies. Brain Cogn 2008;68:241–54.
27. Han SB, Yang HK, Hyon JY, Seo JM, Lee JH, Lee IB, et al. Efficacy of a computerized optokinetic nystagmus test in prediction of visual acuity of better than 20/200. Invest Ophthalmol Vis Sci 2011;52:7492–7.
28. Choi YS, Na HG, Song SY, Kim YD, Bae CH. Clinical signifi-

cance of saccade test, smooth pursuit test, and optokinetic nystagmus test in nystagmography. Yeungnam Univ J Med 2017;34:29–36.
29. Min KK, Ha JS, Kim MJ, Cho CH, Cha HE, Lee JH. Clinical use of subjective visual horizontal and vertical in patients of unilateral vestibular neuritis. Otol Neurotol 2007;28:520–5.
30. Okinaka Y, Sekitani T, Okazaki H, Miura M, Tahara T. Progress of caloric response of vestibular neuronitis. Acta Otolaryngol Suppl 1993;503:18–22.
31. Rosengren SM, Colebatch JG, Young AS, Govender S, Welgampola MS. Vestibular evoked myogenic potentials in practice: methods, pitfalls and clinical applications. Clin Neurophysiol Pract 2019;4:47–68.
32. Shim DB, Song MH, Park HJ. Typical sensory organization test findings and clinical implication in acute vestibular neuritis. Auris Nasus Larynx 2018;45:916–21.
33. Hong HR, Shim DB, Kim TS, Shim BS, Ahn JH, Chung JW, et al. Results of caloric and sensory organization testing of dynamic posturography in migrainous vertigo: comparison with Meniere's disease and vestibular neuritis. Acta Otolaryngol 2013;133:1236–41.
34. Ahmed MF, Goebel JA, Sinks BC. Caloric test versus rotational sinusoidal harmonic acceleration and step-velocity tests in patients with and without suspected peripheral vestibulopathy. Otol Neurotol 2009;30:800–5.
35. Hamid MA. Clinical value of sinusoidal harmonic acceleration test results. Site of lesion and side of lesion. Neurol Clin 1990;8:287–95.
36. Karlberg M, Annertz M, Magnusson M. Acute vestibular neuritis visualized by 3-T magnetic resonance imaging with high-dose gadolinium. Arch Otolaryngol Head Neck Surg 2004;130:229–32.
37. Linstrom CJ. Office management of the dizzy patient. Otolaryngol Clin North Am 1992;25:745–80.
38. Baloh RW. Clinical practice. Vestibular neuritis. N Engl J Med 2003;348:1027–32.
39. Ariyasu L, Byl FM, Sprague MS, Adour KK. The beneficial effect of methylprednisolone in acute vestibular vertigo. Arch Otolaryngol Head Neck Surg 1990;116:700–3.
40. Sjögren J, Magnusson M, Tjernström F, Karlberg M. Steroids for acute vestibular neuronitis-the earlier the treatment, the better the outcome? Otol Neurotol 2019;40:372–4.
41. Shupak A, Issa A, Golz A, Margalit Kaminer, Braverman I. Prednisone treatment for vestibular neuritis. Otol Neurotol 2008;29:368–74.
42. Goudakos JK, Markou KD, Psillas G, Vital V, Tsaligopoulos M. Corticosteroids and vestibular exercises in vestibular neuritis. Single-blind randomized clinical trial. JAMA Otolaryngol Head Neck Surg 2014;140:434–40.
43. Strupp M, Zingler VC, Arbusow V, Niklas D, Maag KP, Dieterich M, et al. Methylprednisolone, valacyclovir, or the combination for vestibular neuritis. N Engl J Med 2004;351:354–61.
44. Ramos Alcocer R, Ledezma Rodríguez JG, Navas Romero A, Cardenas Nuñez JL, Rodríguez Montoya V, Deschamps JJ, et al. Use of betahistine in the treatment of peripheral vertigo. Acta Otolaryngol 2015;135:1205–11.
45. Lacour M, Helmchen C, Vidal PP. Vestibular compensation: the neuro-otologist's best friend. J Neurol 2016;263(Suppl 1):S54–64.
46. McDonnell MN, Hillier SL. Vestibular rehabilitation for unilateral peripheral vestibular dysfunction. Cochrane Database Syst Rev 2015;1:CD005397.
47. Heskin-Sweezie R, Titley HK, Baizer JS, Broussard DM. Type B GABA receptors contribute to the restoration of balance during vestibular compensation in mice. Neuroscience 2010;169:302–14.
48. Igarashi M. Vestibular compensation. An overview. Acta Otolaryngol Suppl 1984;406:78–82.
49. Rossi-Izquierdo M, Santos-Pérez S, Soto-Varela A. What is the most effective vestibular rehabilitation technique in patients with unilateral peripheral vestibular disorders? Eur Arch Otorhinolaryngol 2011;268:1569–74.
50. Hillier S, McDonnell M. Is vestibular rehabilitation effective in improving dizziness and function after unilateral peripheral vestibular hypofunction? An abridged version of a Cochrane Review. Eur J Phys Rehabil Med 2016;52:541–56.
51. Han BI, Song HS, Kim JS. Vestibular rehabilitation therapy: review of indications, mechanisms, and key exercises. J Clin Neurol 2011;7:184–96.
52. Eleftheriadou A, Skalidi N, Velegrakis GA. Vestibular rehabilitation strategies and factors that affect the outcome. Eur Arch Otorhinolaryngol 2012;269:2309–16.

 https://doi.org/10.12701/yujm.2021.01228

Review article

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):89-97
https://doi.org/10.12701/jyms.2021.01669

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Coronavirus disease 2019 (COVID-19) vaccine platforms: how novel platforms can prepare us for future pandemics: a narrative review

Jae Kyung Lee, Ok Sarah Shin

BK21 Graduate Program, Department of Biomedical Sciences, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea

More than 2 years after the explosion of the coronavirus disease 2019 (COVID-19) pandemic, extensive efforts have been made to develop safe and efficacious vaccines against infections with severe acute respiratory syndrome coronavirus 2. The pandemic has opened a new era of vaccine development based on next-generation platforms, including messenger RNA (mRNA)-based technologies, and paved the way for the future of mRNA-based therapeutics to provide protection against a wide range of infectious diseases. Multiple vaccines have been developed at an unprecedented pace to protect against COVID-19 worldwide. However, important knowledge gaps remain to be addressed, especially in terms of how vaccines induce immunogenicity and efficacy in those who are elderly. Here, we discuss the various vaccine platforms that have been utilized to combat COVID-19 and emphasize how these platforms can be a powerful tool to react quickly to future pandemics.

Keywords: COVID-19; mRNA; Pandemics; SARS-CoV-2; Vaccines

Introduction

According to the World Health Organization (WHO), as of December 2021, there have been more than 260 million confirmed coronavirus disease 2019 (COVID-19) cases, of which over 5 million have resulted in death, and over 7.9 billion doses of vaccines administered worldwide [1]. The Americas remain the region with the greatest number of confirmed COVID-19 cases, accounting for approximately 40% of all reported cases. In the Republic of Korea, over 4,077 of the 496,584 confirmed cases of COVID-19 have resulted in death, and over 42 million vaccine doses have been administered. Due to the rapid global spread of COVID-19, vaccines have been highlighted as the most effective countermeasure to protect the immunocompromised and induce herd immunity to maintain the rate of infection below the transmission threshold.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-strand RNA coronavirus belonging to the *Coronaviridae* family. Its viral genome encodes structural and nonstructural proteins, including the following: nucleocapsid (N), spike (S), membrane (M), and envelope (E) proteins [2]. The SARS-CoV-2 S protein binds to angiotensin-converting enzyme 2 (ACE2), a receptor that is expressed in virtually all organs, including the lungs. Consequently, SARS-CoV-2 can in-

Received: December 14, 2021 • **Revised:** January 17, 2022 • **Accepted:** January 27, 2022
Corresponding author: Ok Sarah Shin, MD
Department of Biomedical Sciences, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea
Tel: +82-2-2626-3280 • Fax: +82-2-2626-1962 • E-mail: oshin@korea.ac.kr

fect more than the respiratory system to cause adverse effects and lead to highly variable host immune responses. The broad biodistribution of SARS-CoV-2 suggests that an ideal vaccine will need to elicit both immunoglobulin (Ig) A and IgG antibodies to protect the mucosal surface of the lungs and prevent systemic circulation of the virus [3].

Starting in early 2020, variants of SARS-CoV-2 emerged to pose an increased threat to global public health, further highlighting the priority of addressing the COVID-19 pandemic with safe and effective prophylactic and therapeutic strategies. Currently, the following five variants of SARS-CoV-2 have been classified as variants of concern (VOCs) by the WHO: alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529) [4]. VOCs are assessed according to the degree of significance they have on global public health in terms of increased transmissibility, increased virulence, and whether the variants pose a threat to the currently available diagnostic procedures, vaccines, and therapeutic measures. The omicron (B.1.1.529) variant, which was designated as a VOC by the WHO in November 2021, possesses multiple mutations, including those in the spike protein, which have made the variant highly divergent, and COVID-19 vaccines that are currently available confer reduced protection against infection and symptomatic disease due to the omicron variant [5]. More importantly, the omicron variant has been declared the predominant strain among emerging COVID-19 cases in the United States [6]. Several lineages of the omicron variant have currently been identified and further monitoring is necessary to improve the preparedness and response strategies for addressing current and future variants of COVID-19.

COVID-19 vaccine development has relied on multiple platforms to combat the pandemic. Here, we discuss different strategies of COVID-19 vaccines, including traditional vaccine development strategies based on whole-virus vaccines, live or attenuated, in addition to technologies based on nucleic acid, viral protein subunit, and nonreplicating viral vectors (Fig. 1).

Multiple vaccine platforms

Virus-based vaccines include live-attenuated and inactivated viruses, which lack pathogenic characteristics and cannot mount a complete infection, respectively. Protein-based vaccines consist of purified proteins from viruses or infected cells, recombinant proteins, or virus-like particles, the latter of which are composed of structural proteins capable of forming virus particles without the viral genome.

Advances in molecular biology and vaccinology have also created novel platform technologies for vaccine development. These next-generation platforms rely on viral genome sequences that encode viral proteins, rather than the virus itself, for vaccine development, which is more adaptable for mass production during public

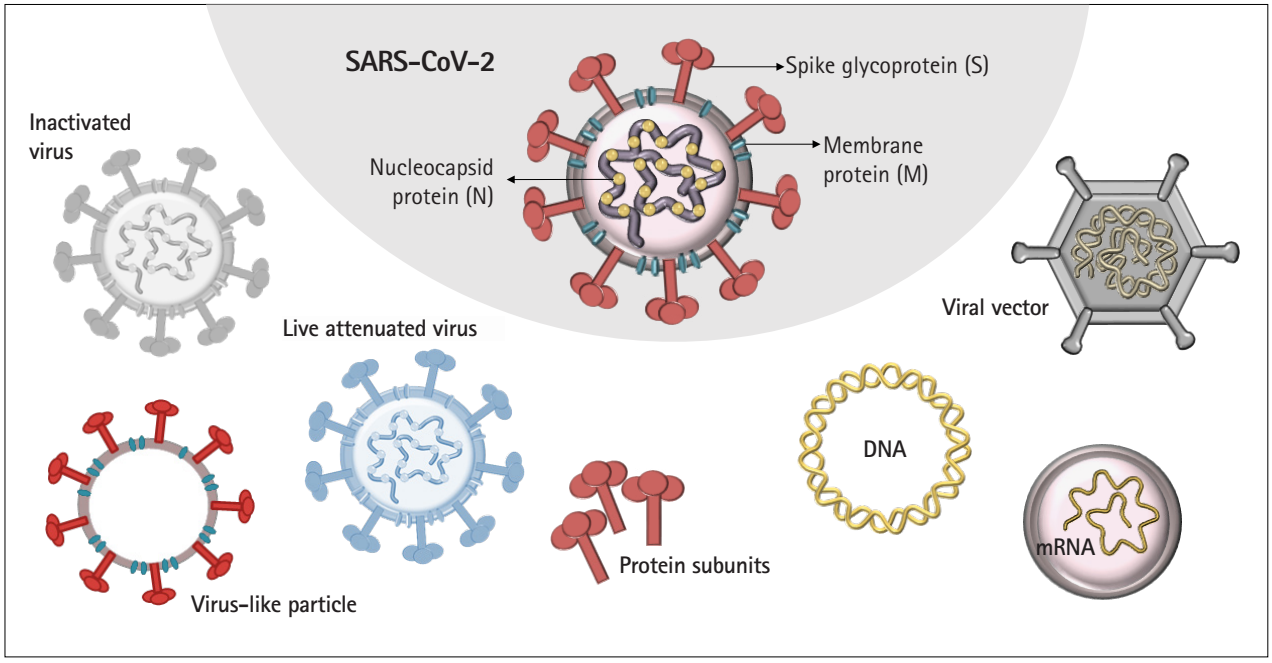

Fig. 1. Different strategies to develop coronavirus disease 2019 (COVID-19) vaccines. Classical and next-generation platform-based vaccines that have been developed as a countermeasure to the COVID-19 pandemic are shown. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; mRNA, messenger RNA.

 https://doi.org/10.12701/jyms.2021.01669

health emergencies, such as the COVID-19 pandemic. Table 1 outlines the advantages and disadvantages of various vaccine platforms that have been utilized for the development of COVID-19 vaccines. Reports have indicated that the currently available vaccines are associated with minor side effects, including headache, nausea, and pain/soreness at the injection site, although rare and unusual adverse events have also been observed for specific types of COVID-19 vaccines [7].

Inactivated vaccines

Inactivated vaccines employ viruses that can no longer replicate because of heat or chemical treatment. Currently, inactivated vaccines against viruses, such as influenza virus, poliovirus, and hepatitis A virus, are available. VaxigripTetra (Sanofi Pasteur, Lyon, France) is a quadrivalent inactivated influenza vaccine that has been available since 2016. The vaccine contains both A strains (H1N1 and H3N2) and B strains (Victoria and Yamagata) and has been shown to be efficacious and safe in both children and pregnant women [8,9]. Multiple inactivated hepatitis A vaccines, such as VAQTA (Merck, Branchburg, NJ, USA), AVAXIM (Sanofi Pasteur), HAVRIX (GSK, Brentford, UK), and Epaxal (Janssen Biotech Inc., Horsham, PA, USA), are currently available. While hepatitis A vaccinations usually consist of a two-dose schedule, Ott and Wiersma [10] have shown that a single dose of inactivated hepatitis A vaccines can induce anti-hepatitis A virus antibodies that persist for approximately 11 years. In terms of protection against polio, the Centers for Disease Control and Prevention recommends four doses of polio vaccines at specified ages. The inactivated poliovirus vaccine is currently the only vaccine against polio that is administered in the United States, as the oral poliovirus vaccine is associated with a risk of vaccine-derived poliovirus [11]. IPOL (Sanofi Pasteur) is an inactivated vaccine manufactured from three types (1, 2, and 3) of poliovirus that have been shown to cause poliomyelitis.

CoronaVac (Sinovac Life Sciences Co., Ltd., Beijing, China) is an inactivated whole-virus vaccine that was initially approved for emergency use in China, but further studies were deemed necessary to determine the durability of the elicited immune response [12]. Results from a phase III clinical trial in Turkey revealed an

Table 1. Advantages and disadvantages outlined for each vaccine platform

Vaccine platform	Advantage	Disadvantage
Inactivated virus	High safety profile, even for the immunocompromised High stability	Low immunogenicity requires boosters High caution for safety testing required for production Difficult to scale up in short time
Live attenuated virus	Develops prolonged immunity High immunogenicity	Possible side effects involving regression to virulence strain Not recommended for immunocompromised patients High caution for safety testing
Viral vector	High specificity of antigen delivery to target cells High antigen expression Single dose confers long-term protection	Virus vector itself may elicit immune response Potential integration of the viral genome into the host genome
DNA	Design based on genetic sequencing Easy manufacturing Lower cost of production DNA is temperature stable and cold-chain free	Potential integration to human genome remains concern
mRNA	Relatively low-cost and easy manufacturing Translation of mRNA occurs in the cytosol of the host cell, thus reducing the risk of integration into the host genome	Need efficient delivery tools such as nanoparticles due to instability Multiple doses may be necessary for booster effect
Protein subunit	High stability Safe manufacturing procedure Allows selection of specific antigens to be combined for a multivalent vaccine Highly adaptable	Low immunogenicity requires boosters Adjuvants required for robust immune response Time consuming to determine appropriate antigen

mRNA, messenger RNA.

83.5% efficacy 14 days or more after the administration of the second dose of CoronaVac [13]. BBIBP-CorV (Sinopharm, Beijing, China) is another inactivated COVID-19 vaccine that is administered as a two-dose immunization [14]. Phase I/II trial results have shown that this inactivated vaccine is safe and well tolerated, in addition to inducing robust humoral responses [15]. High titers of neutralizing antibodies were reported to be induced in participants vaccinated with inactivated whole-virus vaccines [16]. In terms of vaccine efficacy against VOCs, a 59% vaccine efficacy against infection with the delta variant was reported following a two-dose vaccination with CoronaVac [17].

Unfortunately, technical challenges exist with inactivated whole-virus vaccines, especially in terms of the risk of disease outbreak and the inactivation process that can potentially damage antigens and result in suboptimal immunogenicity. There is also a biosafety level 3 requirement to manufacture inactivated whole-virus vaccines. Furthermore, inactivated vaccines are not known to activate cellular immune responses, and no T cell responses were reported following vaccination with CoronaVac [12]. Therefore, adjuvants and multiple booster doses are crucial to enhance the immune response elicited by inactivated vaccines, and further studies are needed to determine the effect of booster doses on inactivated whole-virus COVID-19 vaccines.

Viral vector vaccines

Advances have allowed the genetic manipulation of viruses into suitable vectors that can deliver genetic material. The viruses used as vaccine vectors must be harmless and prompt the target cells to produce antigens that can activate the immune response without causing disease. Among the various viruses, adenoviruses have been the most studied and have shown potential. Adenoviral vectors are built by replacing the viral genes involved in replication with a gene of choice. Most adenoviral vectors are constructed by deleting the E1 and E3 genes, which are involved in viral replication and modulation of the host immune response, respectively [18]. Furthermore, adenoviral vectors are commonly used platforms in cancer gene therapy, which employs adenoviruses engineered to selectively replicate in and kill tumor cells [19]. Antigens delivered by adenoviral vectors after a single immunization have been shown to induce both cellular and humoral immunity, with the second immunization mounting a long-lasting immune response [20,21]. In designing adenovirus vaccine vectors, it is important to select adenovirus serotypes that do not elicit an immune response in humans from preexisting immunity.

Adenoviral vector COVID-19 vaccines exploit adenoviruses to create viral vectors carrying DNA sequences encoding the full-length S protein of SARS-CoV-2. Since the S protein binds to ACE2 for cellular entry, vaccines that produce antibodies able to bind the S protein are expected to neutralize the viral infection [22]. ChAdOX1, AstraZeneca's COVID-19 vaccine (AstraZeneca, Cambridge, UK) uses a recombinant adenovirus derived from chimpanzees to produce adenoviral vectors carrying the full-length S protein sequence [23]. ChAdOX1 was shown to induce strong cellular immunity, especially in terms of increased effector T cell responses specific to the S protein. A second dose was administered 8 to 12 weeks after the first dose is the recommended vaccination schedule set by the WHO. A study has shown that increasing the interval between primary and booster doses of ChAdOX1 beyond 12 weeks resulted in antibody titers that were higher than those mounted by a second dose administered within 6 weeks of the initial vaccination [24].

Ad26.COV2.S, Janssen Biotech's COVID-19 vaccine is an S protein-based adenoviral serotype 26 vector vaccine that elicited strong Th1-skewed cellular immune responses during clinical trials [25]. The Janssen vaccine expresses the prefusion form of the S antigen that has undergone stabilizing substitutions [26]. Gam-COVID-Vac (also known as Sputnik V), an adenovirus vector vaccine produced by the Russian Gamaleya Research Institute of Epidemiology and Microbiology, is distinct from the previously mentioned vaccines in terms of its heterologous prime-boost approach. Gam-COVID-Vac utilizes two different adenoviral vectors, Ad26 and Ad5, which are administered individually 21 days apart [27]. CELLID (Seoul, Korea) has also developed AdCLD-CoV19, an adenoviral vector vaccine based on the human Ad type 5/35 vector containing the gene for the S protein of SARS-CoV2, which has been approved for phase I/II trials in the Republic of Korea.

To circumvent the challenges associated with preexisting immunity against certain human adenovirus serotypes, prime-boost regimens, such as those used for Sputnik V, have mainly relied on longer intervals (> 12 weeks) or utilization of different serotypes. However, further studies that utilize a combination of different strategies are needed to improve adenoviral vector vaccines.

Although rare and unusual, thrombocytopenia was among the adverse events reported in persons vaccinated with ChAdOX1 and Ad26.COV2.S, particularly in young women [28,29].

Messenger RNA vaccines

Prior to the COVID-19 pandemic, nucleic acid-based vaccine candidates against diseases were unable to progress beyond clinical trials. Nucleic acid-based vaccines have the advantage of a shorter development period following sequence selection when compared to

virus- or protein-based vaccines. Vaccine technologies utilized by nucleic acid-based platforms also take advantage of nanoparticles in terms of their small size and ability to enter cells and deliver nucleic acids via DNA or messenger RNA (mRNA) vaccines. Lipid nanoparticles can encapsulate genomic materials that carry antigen-encoding sequences.

mRNA-based vaccines that have been approved for use include the Pfizer-BioNTech COVID-19 vaccine (BNT162b2; Pfizer Inc., New York, NY, USA) and Moderna COVID-19 vaccine (mRNA-1273; Moderna Inc., Cambridge, MA, USA). Both rely on the viral genomic sequence encoding the subunits of the S protein of SARS-CoV-2.

The Pfizer-BioNTech COVID-19 vaccine, or Comirnaty, consists of a lipid nanoparticle that encapsulates mRNA encoding a modified, full-length SARS-CoV-2 S protein that has been mutated to maintain a prefusion conformation [30,31]. The vaccine requires two doses to be administered 21 days apart, and studies have reported a 95% efficacy, with protection being observed within 12 days after the first dose. A 6-month follow-up study on the safety profile and need for booster dosing demonstrated a decline in vaccine-mediated protection, with the vaccine efficacy waning approximately 6% every 2 months following the second dose in participants aged 12 years and older [32]. Consequently, a single booster dose of Comirnaty following the primary series has been shown to increase neutralizing antibody titers.

In addition, T cell responses have been shown to be important in controlling SARS-CoV-2 infections, and the prime-boost vaccination regimen with Comirnaty was reported to induce strong Th1-biased T cell responses consisting of high levels of interferon gamma and interleukin-2 [33]. With the recent emergence of the omicron variant, two doses of Comirnaty were reported by Pfizer to confer protection against any severe disease, although a booster dose is recommended. Since the majority of the epitopes on the S protein of the omicron variant are predicted to maintain their ability for human leukocyte antigen-epitope binding, vaccines such as Comirnaty that focus on the S protein are expected to elicit a sufficiently robust T cell immunity against VOCs such as omicron [34-36]. A study on the effectiveness of Pfizer's Comirnaty and AstraZeneca's ChAdOX1 against the delta (B.1.617.2) variant demonstrated that the efficacy of both vaccines was lower for the delta variant than for the alpha (B.1.1.7) variant [37]. Furthermore, a heterologous prime-boost vaccination with ChAdOX1 (prime) and Comirnaty (boost) was reported to induce robust humoral and cellular immune responses with T cells that were reactive to variants, including alpha, beta, gamma, and delta [38]. Recent findings have shown that a booster shot with Comirnaty was associated with reduced rates of infection and severe illness across different age groups [39].

The Moderna COVID-19 vaccine (mRNA-1273) contains mRNA encoding the prefusion form of the S antigen with two mutations at amino acids 986 and 987 to stabilize the S protein in its prefusion conformation [31]. The Moderna COVID-19 vaccine schedule consists of a two-dose series separated by 28 days. Both of the previously mentioned mRNA vaccines do not include the use of an adjuvant, as the RNA and lipids themselves have been reported to have adjuvant properties [40]. High levels of neutralizing antibodies and a Th1-skewed T cell response were reported following vaccination with mRNA-1273, with efficacy of approximately 93% for preventing COVID-19, while a higher vaccine efficacy of 98% was observed for preventing severe COVID-19 starting 14 days after the second dose [41,42].

A comparative study on the vaccine efficacy of Moderna's mRNA-1273, Pfizer-BioNTech's Comirnaty, and Janssen's Ad26.COV2.S revealed that the two mRNA vaccines (mRNA-1273 and Comirnaty) had higher vaccine efficacy and induced higher post-vaccination anti-SARS-CoV-2 antibody levels than Janssen's adenoviral vector vaccine (Ad26,COV2.S) in healthy adults [43].

Evaluation of the safety profiles revealed that adverse events, while rare, were associated with the mRNA vaccines of both Moderna and Pfizer-BioNTech. Multiple cases of myocarditis were reported following vaccination, with the highest risk observed in young men between the ages of 20 and 34 years [44,45]. In addition to myocarditis, Bell's palsy after vaccination with either mRNA vaccine has been reported [46-48].

DNA vaccines

DNA vaccines have already been integrated into veterinary practice to treat diseases, including tuberculosis [49], avian influenza [50], and rabies [51]. Several vaccine candidates utilizing DNA-based platforms are currently undergoing clinical trials. Genexine's GX-19 (Genexine, Seongnam, Korea), which contains genes encoding both the S and N proteins, and GeneOne Life Science's GLS-5310 (GeneOne Life Science, Seoul, Korea) are DNA vaccines that have been approved for phase I and phase IIa clinical trials in the Republic of Korea. Moreover, the International Vaccine Institute (Seoul, Korea) has collaborated with INOVIO Pharmaceuticals (Plymouth Meeting, PA, USA) to advance clinical trials of INO-4800, a DNA vaccine that has been shown to induce cellular and humoral immune responses after the second immunization [52].

While mRNA can be directly translated once inside the cell, DNA must undergo nuclear translocation prior to mRNA being transcribed and exported to the cytoplasm for translation. As a re-

sult, mRNA has a higher translation efficiency than DNA when transfected. However, DNA is more stable than mRNA, and expression of the latter is shorter-lived. These type-specific pros and cons of nucleic acids highlight the importance of considering both stability and translation efficiency in terms of developing a vaccine that can produce effective antigens capable of mounting an immune response.

Protein subunit vaccines

Vaccine technologies based on protein subunits are also viable vaccine candidates for protection against SARS-CoV-2 infection. Novavax's recombinant SARS-CoV-2 S protein nanoparticle vaccine, NVX-CoV2373 (Novavax, Gaithersburg, MD, USA), includes the prefusion form of the full-length S protein that has been modified for stabilization and resistance to cleavage. The vaccine is administered with Matrix-M adjuvant (Novavax), which has previously been shown to enhance immunogenicity of the influenza vaccine [53-55]. Two doses of NVX-CoV2373 were reported to confer approximately 89% protection against SARS-CoV-2 infection [56]. Subunit vaccines can also include adjuvants to boost immune responses by stimulating the desired receptors responsible for sensing pathogens or danger signals [57]. SK Bioscience's recombinant protein nanoparticle vaccine candidate GBP510 (SK Bioscience, Seongnam, Korea), which contains alum as an adjuvant, and EuCorVac-19, a recombinant protein vaccine manufactured by EuBiologics (Seoul, Korea), are both currently undergoing phase I/II trials in the Republic of Korea.

Despite the long strides that have been made by the fast-paced development, emergency approval, and administration of the previously mentioned vaccines, the variability in host immune responses, which results in patients who range from asymptomatic to critically ill, remains a difficult obstacle that requires long-term follow-up studies postvaccination.

Conclusion

Although multiple COVID-19 vaccines are now available across the globe, we still face several challenges concerning long-term vaccine efficacy, as well as effectiveness against present and future variants. It is essential to plan for the development of modified vaccines that could protect against vaccine-resistant variants, as we are now witnessing the emergence of VOCs that have increased the transmissibility and virulence of COVID-19. Therefore, the combined use of the diverse platforms for COVID-19 vaccines that are now available will aid in the development of vaccines against current and future variants.

While the global morbidity and mortality caused by COVID-19 emphasize the need for vaccination, adverse events remain a risk associated with the currently available vaccines. While most side effects following vaccination are mild, such as headache and pain/soreness at the injection site, severe adverse events such as myocarditis and thrombocytopenia have also been reported, particularly in young women and men. In the future, we need to focus on developing novel vaccine platforms that are associated with lower risks of adverse events and increasing our efforts toward establishing a universal coronavirus vaccine that can confer broad protection against a diverse number of coronaviruses, including all variants, to increase our preparedness for future pandemics.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

This research was funded by the Basic Science Research Program of the National Research Foundation of Korea (NRF) by the Ministry of Science, ICT & Future Planning (NRF-2019R1A2C1005961).

Author contributions

Conceptualization, Formal analysis: JKL, OSS; Funding acquisition, Supervision: OSS; Investigation, Methodology: JKL; Writing-original draft: JKL; Writing-review & editing: OSS.

ORCID

Jae Kyung Lee, https://orcid.org/0000-0002-9641-8473
Ok Sarah Shin, https://orcid.org/0000-0002-3977-2492

References

1. World Health Organization (WHO). WHO coronavirus (COVID-19) dashboard [Internet]. Geneva: WHO; 2021 [cited 2021 Dec 14]. https://covid19.who.int/.
2. Stadler K, Masignani V, Eickmann M, Becker S, Abrignani S, Klenk HD, et al. SARS: beginning to understand a new virus. Nat Rev Microbiol 2003;1:209–18.
3. Janeway Jr CA, Travers P, Walport M, Shlomchik MJ. The distribution and functions of immunoglobulin isotypes. In: Janeway Jr CA, Travers P, Walport M, Shlomchik MJ, editors. Immunobiology: the immune system in health and disease. 5th ed.

New York: Garland Science; 2001.
4. World Health Organization (WHO). Tracking SARS-CoV-2 variants [Internet]. Geneva: WHO; 2021 [cited 2021 Dec 14]. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.
5. World Health Organization (WHO). Weekly epidemiological update on COVID-19-25 [Internet]. Geneva: WHO; 2022 [cited 2022 Jan 17]. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-january-2022.
6. Centers for Disease Control and Prevention (CDC). COVID data tracker: variant proportions [Internet]. Atlanta: CDC; 2022 [cited 2022 Jan 17]. https://covid.cdc.gov/covid-data-tracker/#monitoring-varaint-heading.
7. Beatty AL, Peyser ND, Butcher XE, Cocohoba JM, Lin F, Olgin JE, et al. Analysis of COVID-19 vaccine type and adverse effects following vaccination. JAMA Netw Open 2021;4:e2140364.
8. Bansal A, Trieu MC, Mohn KGI, Cox RJ. Safety, immunogenicity, efficacy and effectiveness of inactivated influenza vaccines in healthy pregnant women and children under 5 years: an evidence-based clinical review. Front Immunol 2021;12:744774.
9. Pepin S, Dupuy M, Borja-Tabora CF, Montellano M, Bravo L, Santos J, et al. Efficacy, immunogenicity, and safety of a quadrivalent inactivated influenza vaccine in children aged 6-35 months: a multi-season randomised placebo-controlled trial in the Northern and Southern hemispheres. Vaccine 2019;37:1876–84.
10. Ott JJ, Wiersma ST. Single-dose administration of inactivated hepatitis A vaccination in the context of hepatitis A vaccine recommendations. Int J Infect Dis 2013;17:e939–44.
11. Centers for Disease Control and Prevention (CDC). Polio vaccination [Internet]. Atlanta: CDC; 2018 [cited 2022 Jan 17]. https://www.cdc.gov/vaccines/vpd/polio/index.html.
12. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21:181–92.
13. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021;398:213–22.
14. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, et al. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell 2020;182:713–21.
15. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis 2021;21:39–51.
16. Guo W, Duan K, Zhang Y, Yuan Z, Zhang YB, Wang Z, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18 years or older: a randomized, double-blind, placebo-controlled, phase 1/2 trial. EClinicalMedicine 2021;38:101010.
17. Li XN, Huang Y, Wang W, Jing QL, Zhang CH, Qin PZ, et al. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. Emerg Microbes Infect 2021;10:1751–9.
18. Russell WC. Adenoviruses: update on structure and function. J Gen Virol 2009;90(Pt 1):1–20.
19. Buller RE, Runnebaum IB, Karlan BY, Horowitz JA, Shahin M, Buekers T, et al. A phase I/II trial of rAd/p53 (SCH 58500) gene replacement in recurrent ovarian cancer. Cancer Gene Ther 2002;9:553–66.
20. Tatsis N, Ertl HC. Adenoviruses as vaccine vectors. Mol Ther 2004;10:616–29.
21. Dolzhikova IV, Zubkova OV, Tukhvatulin AI, Dzharullaeva AS, Tukhvatulina NM, Shcheblyakov DV, et al. Safety and immunogenicity of GamEvac-Combi, a heterologous VSV- and Ad5-vectored Ebola vaccine: an open phase I/II trial in healthy adults in Russia. Hum Vaccin Immunother 2017;13:613–20.
22. Astuti I. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diabetes Metab Syndr 2020;14:407–12.
23. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020;396:467–78.
24. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet 2021;397:881–91.
25. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim results of a phase 1-2a trial of Ad26.COV2.S COVID-19 vaccine. N Engl J Med 2021;384:1824–35.
26. Bos R, Rutten L, van der Lubbe JE, Bakkers MJ, Hardenberg G, Wegmann F, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. NPJ

Vaccines 2020;5:91.
27. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 2021;397:671–81.
28. Eichinger S, Warkentin TE, Greinacher A. Thrombotic thrombocytopenia after ChAdOx1 nCoV-19 vaccination: reply. N Engl J Med 2021;385:e11.
29. Health Alert Network; Centers for Disease Control and Prevention (CDC). Emergency preparedness and response: cases of cerebral venous sinus thrombosis with thrombocytopenia after receipt of the Johnson & Johnson COVID-19 vaccine [Internet]. Atlanta: CDC; 2021 [cited 2022 Jan 17]. https://emergency.cdc.gov/han/2021/han00442.asp.
30. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603–15.
31. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367:1260–3.
32. Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine through 6 months. N Engl J Med 2021;385:1761–73.
33. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature 2021;595:572–7.
34. Ahmed SF, Quadeer AA, McKay MR. SARS-CoV-2 T cell responses elicited by COVID-19 vaccines or infection are expected to remain robust against Omicron. Viruses 2022;14:79.
35. Tarke A, Sidney J, Methot N, Yu ED, Zhang Y, Dan JM, et al. Impact of SARS-CoV-2 variants on the total CD4+ and CD8+ T cell reactivity in infected or vaccinated individuals. Cell Rep Med 2021;2:100355.
36. Stanojevic M, Geiger A, Ostermeier B, Sohai D, Lazarski C, Lang H, et al. Spike-directed vaccination elicits robust spike-specific T-cell response, including to mutant strains. Cytotherapy 2022;24:10–5.
37. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (Delta) variant. N Engl J Med 2021;385:585–94.
38. Groß R, Zanoni M, Seidel A, Conzelmann C, Gilg A, Krnavek D, et al. Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T cell reactivity against prevalent SARS-CoV-2 variants. EBioMedicine 2022;75:103761.
39. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against COVID-19 by BNT162b2 booster across age groups. N Engl J Med 2021;385:2421–30.
40. Perrie Y, Crofts F, Devitt A, Griffiths HR, Kastner E, Nadella V. Designing liposomal adjuvants for the next generation of vaccines. Adv Drug Deliv Rev 2016;99(Pt A):85–96.
41. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 2020;383:2427–38.
42. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021;385:1774–85.
43. Self WH, Tenforde MW, Rhoads JP, Gaglani M, Ginde AA, Douin DJ, et al. Comparative effectiveness of moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) vaccines in preventing COVID-19 hospitalizations among adults without immunocompromising conditions: United States, March-August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1337–43.
44. Castiello T, Georgiopoulos G, Finocchiaro G, Claudia M, Gianatti A, Delialis D, et al. COVID-19 and myocarditis: a systematic review and overview of current challenges. Heart Fail Rev 2022;27:251–61.
45. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA COVID-19 vaccine in a nationwide setting. N Engl J Med 2021;385:1078–90.
46. Colella G, Orlandi M, Cirillo N. Bell's palsy following COVID-19 vaccination. J Neurol 2021;268:3589–91.
47. Repajic M, Lai XL, Xu P, Liu A. Bell's Palsy after second dose of Pfizer COVID-19 vaccination in a patient with history of recurrent Bell's palsy. Brain Behav Immun Health 2021;13:100217.
48. Ozonoff A, Nanishi E, Levy O. Bell's palsy and SARS-CoV-2 vaccines. Lancet Infect Dis 2021;21:450–2.
49. Teixeira FM, Teixeira HC, Ferreira AP, Rodrigues MF, Azevedo V, Macedo GC, et al. DNA vaccine using Mycobacterium bovis Ag85B antigen induces partial protection against experimental infection in BALB/c mice. Clin Vaccine Immunol 2006;13:930–5.
50. Kodihalli S, Kobasa DL, Webster RG. Strategies for inducing protection against avian influenza A virus subtypes with DNA vaccines. Vaccine 2000;18:2592–9.
51. Rai N, Kaushik P, Rai A. Development of rabies DNA vaccine using a recombinant plasmid. Acta Virol 2005;49:207–10.

52. Tebas P, Yang S, Boyer JD, Reuschel EL, Patel A, Christensen-Quick A, et al. Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: a preliminary report of an open-label, Phase 1 clinical trial. EClinicalMedicine 2021;31:100689.
53. Pallesen J, Wang N, Corbett KS, Wrapp D, Kirchdoerfer RN, Turner HL, et al. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci U S A 2017;114:E7348–57.
54. Magnusson SE, Altenburg AF, Bengtsson KL, Bosman F, de Vries RD, Rimmelzwaan GF, et al. Matrix-M™ adjuvant enhances immunogenicity of both protein- and modified vaccinia virus Ankara-based influenza vaccines in mice. Immunol Res 2018;66:224–33.
55. Reimer JM, Karlsson KH, Lövgren-Bengtsson K, Magnusson SE, Fuentes A, Stertman L. Matrix-M™ adjuvant induces local recruitment, activation and maturation of central immune cells in absence of antigen. PLoS One 2012;7:e41451.
56. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 COVID-19 vaccine. N Engl J Med 2021;385:1172–83.
57. Arunachalam PS, Walls AC, Golden N, Atyeo C, Fischinger S, Li C, et al. Adjuvanting a subunit COVID-19 vaccine to induce protective immunity. Nature 2021;594:253–8.

Original article

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):98-107
https://doi.org/10.12701/yujm.2021.01368

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Storing information of stroke rehabilitation patients using blockchain technology: a software study

Min Cheol Chang

Department of Physical Medicine and Rehabilitation, Yeungnam University College of Medicine, Daegu, Korea

Background: Stroke patients usually experience damage to multiple functions and a long rehabilitation period. Hence, there is a large volume of patient clinical information. It thus takes a long time for clinicians to identify the patient's information and essential pieces of information may be overlooked. To solve this, we stored the essential clinical information of stroke patients in a blockchain and implemented the blockchain technology using the Java programming language.
Methods: We created a mini blockchain to store the medical information of patients using the Java programming language.
Results: After generating a unique pair of public/private keys for identity verification, a patient's identity is verified by applying the Elliptic Curve Digital Signature Algorithm based on the generated keys. When the identity verification is complete, new medical data are stored in the transaction list and the generated transaction is verified. When verification is completed normally, the block hash value is derived using the transaction value and the hash value of the previous block. The hash value of the previous block is then stored in the generated block to interconnect the blocks.
Conclusion: We demonstrated that blockchain can be used to store and deliver the patient information of stroke patients. It may be difficult to directly implement the code that we developed in the medical field, but it can serve as a starting point for the creation of a blockchain system to be used in the field.

Keywords: Blockchain; Information services; Patients; Rehabilitation; Stroke

Introduction

A blockchain, also called a distributed or shared ledger, is a technology through which participants jointly verify, store, distribute, and interconnect data without an authorized third party by generating data in blocks [1,2]. It allows participants to jointly record data by distributing the data to a person-to-person (P2P) network rather than to the central server of a specific organization [1,2]. Those who are permitted to see the ledger read it according to an agreed method, and the transactions are also recorded according to an agreed method. In this way, information can be stored securely without a central server, and the content can be trusted without a third-party guarantee. The applications of blockchain have been expanding to various fields including government, finance, and public data, and its use is also being explored in the medical field [3-5].

Currently, patient medical information is stored on hospital servers, and hospitals cannot easily exchange the patient information stored on such servers with other hospitals because of the risk of a privacy breach [1]. Consequently, when patients are transferred to another hospital, they need to carry their medical information from one hospital to the next. Conversely, if blockchain were used in place of servers, the information would be generated

Received: July 28, 2021 • **Revised:** August 13, 2021 • **Accepted:** August 13, 2021
Corresponding author: Min Cheol Chang, MD
Department of Physical Medicine and Rehabilitation, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-4682 • Fax: +82-53-4231-8694 • E-mail: wheel633@gmail.com

and recorded in block units and then stored on multiple nodes in a distributed manner [6]. This would make hacking practically impossible while allowing hospitals to easily and freely share patient information with other hospitals.

During the rehabilitation of a stroke patient, a large amount of data related to the patient's condition is generated due to the long rehabilitation period [7]. Furthermore, many patients are transferred to different hospitals to receive rehabilitation treatments. When a patient moves to another hospital, the patient or their guardian must receive the printed patient care information from the old hospital and deliver it to the new hospital [1,7]. Doctors check the current and past conditions of transferred patients based on these paper records, which takes a considerable amount of time. Moreover, important pieces of information may be missed due to the large volume of information and because each hospital records patient information in its own way. We believe that blockchain can help to solve this problem.

Based on the previous study [7], we identified the essential information for stroke patients receiving rehabilitation treatment and then used private blockchain network technology to store the information of one patient through the medical information transaction process. Since the personal medical information of patients can be transferred on the network, only the participants who were authorized to use the private blockchain were allowed to write and read the patient medical information.

Methods

We created a mini blockchain to store the medical information of patients using the Java programming language. To actually run the source code written in Java, we installed the Java Development Kit and Eclipse, the most representative integrated Java development environment.

Results

The medical information transaction process is illustrated in Fig. 1.

1. Patient consent

A patient's consent is required before sharing their personal medical information on the network. The procedure for obtaining consent is conducted through an application. Once the patient's consent has been obtained, a unique pair of public/private keys is issued for the patient. The issued keys are stored as files: the private key is stored on the patient's smartphone, and the public key is stored by the medical institutions that participate in the network. In general, keys are stored in a byte format, which is difficult to read or process. However, the format in which the key data are encoded and managed can be conveniently viewed and transmitted using the Base64 algorithm (an encoding algorithm that converts binary data to text). An encoded file is called 'Privacy-Enhanced Mail' and generally has the file extension '.pem'. The keys are randomly generated using the chart number or resident registration number of the patient.

Code: Generation of private and public keys

A unique pair of private/public keys are generated for a given patient using the Elliptic Curve Digital Signature Algorithm (ECDSA) algorithm. The generated keys have the file extension '.pem' and are stored under a specific file name.

Generation of private and public keys using the Elliptic Curve Digital Signature Algorithm

```
// Private and public keys are generated using the ECDSA algorithm and then stored.
// For a detailed version of the ECDSA, we use sect163k1.
public void generate (String privateKeyName, String publicKeyName) throws Exception {
// The ECDSA algorithm of the Bouncy Castle is used.
KeyPairGenerator generator = KeyPairGenerator.getInstance("ECDSA", "BC");
// sect163k1 is the algorithm used to generate the elliptic curve.
ECGenParameterSpec ecsp;
ecsp = new ECGenParameterSpec("sect163k1");
generator.initialize(ecsp, new SecureRandom());
// A random pair of keys is generated using this algorithm.
KeyPair keyPair = generator.generateKeyPair();
System.out.println("A pair of elliptic curve encryption keys was generated.");
// The private and public keys are extracted from the generated keys.
PrivateKey priv = keyPair.getPrivate();
PublicKey pub = keyPair.getPublic();
// The private and public keys are stored under specific file names.
writePemFile(priv, "EC PRIVATE KEY", privateKeyName);
writePemFile(pub, "EC PUBLIC KEY", publicKeyName);
}

// The generated encryption key is save as a file in the .pem class.
private void writePemFile(Key key, String description, String filename) throws FileNotFoundException, IOException{
Pem pemFile = new Pem(key, description);
pemFile.write(filename);
```

(Continued to the next page)

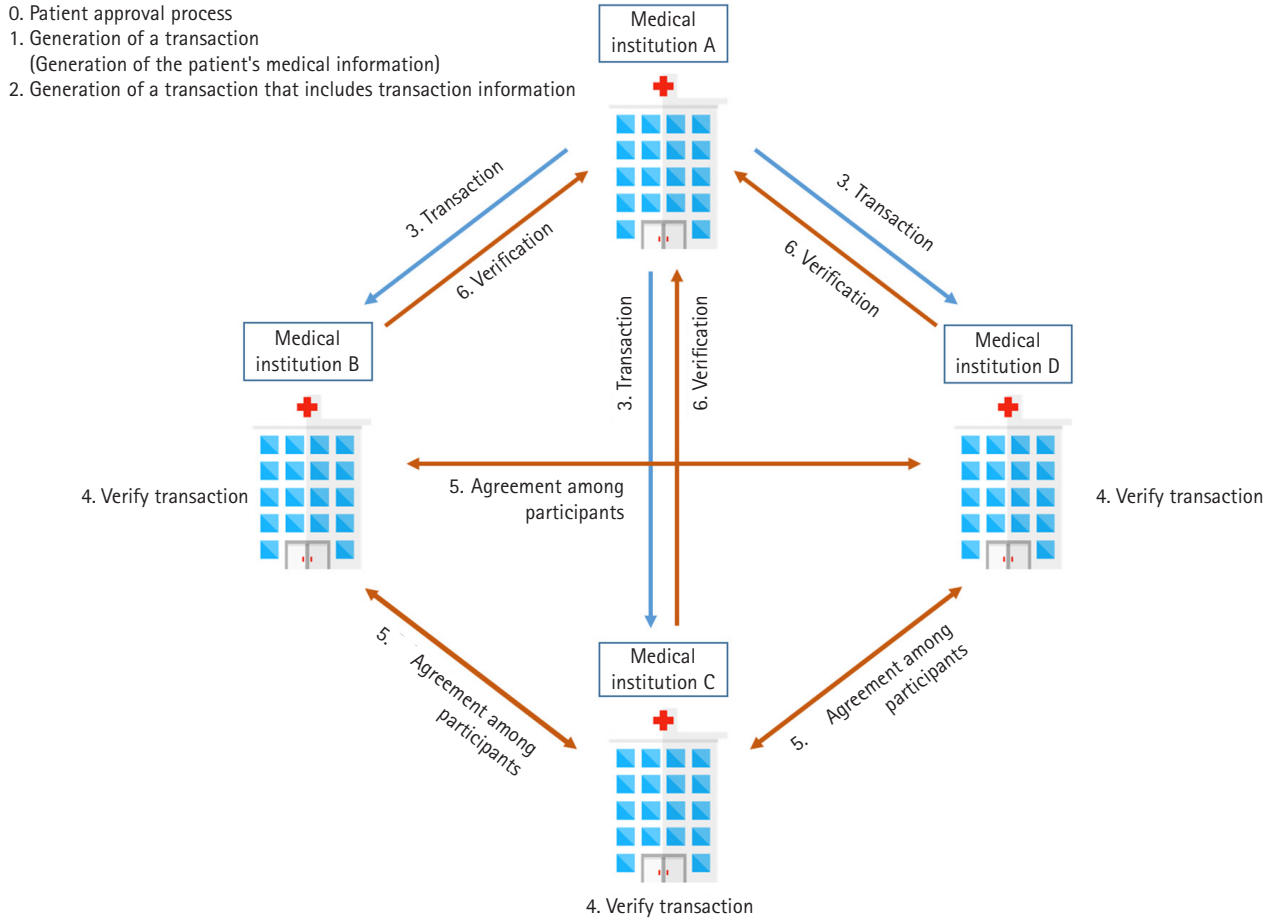

Fig. 1. Application of blockchain technology to medical information: patient identities are verified using the public key-based structure, and the medical records of the verified patients are connected as a chain through the hash value.

```
System.out.println(String.format("Encryption key %s was exported to the file %s.", description, filename));
}
```

When the private and public keys stored in the .pem files are opened, they have the following format.

Format of private and public keys

```
-----BEGIN EC PRIVATE KEY-----
MGwCAQAwEAYHKoZIzj0CAQYFK4EEAAEEVTBTAgEBBBUCoeEILPFbMQIh3CRiHo+S
3++ka8egBwYFK4EEAAGhLgMsAAQCupGyQ46vQ9dG6wtab7xZtJMFdcIGu0fHQR+Z
OnNX8k/xYjkrRjGTBEU=
-----END EC PRIVATE KEY-----

-----BEGIN EC PUBLIC KEY-----
```

(Continued to)

```
MEAwEAYHKoZIzj0CAQYFK4EEAAEDLAAEArqRskOOr0PXRusLWm+8WbSTBXXCBrtH
x0EfmTpzV/JP8WI5K0YxkwRF
-----END EC PUBLIC KEY-----
```

2. Identification

The purpose of the identification process is to verify the identity of patients using a public key-based structure (Fig. 2). The function of the public key-based structure is to manage passwords as pairs of private and public keys using the ECDSA algorithm. Data encrypted with a private key can only be decrypted with the public key with which it is paired. The private key is encrypted using the patient's chart number or resident registration number and then decrypted by reading the public key. If the patient's public key or private key does not exist or has been manipulated or damaged, identity verification fails, and it is impossible to access the patient's medical information.

Code: Identity verification process

The private and public keys of a given patient are read, and their va-

 https://doi.org/10.12701/yujm.2021.01368

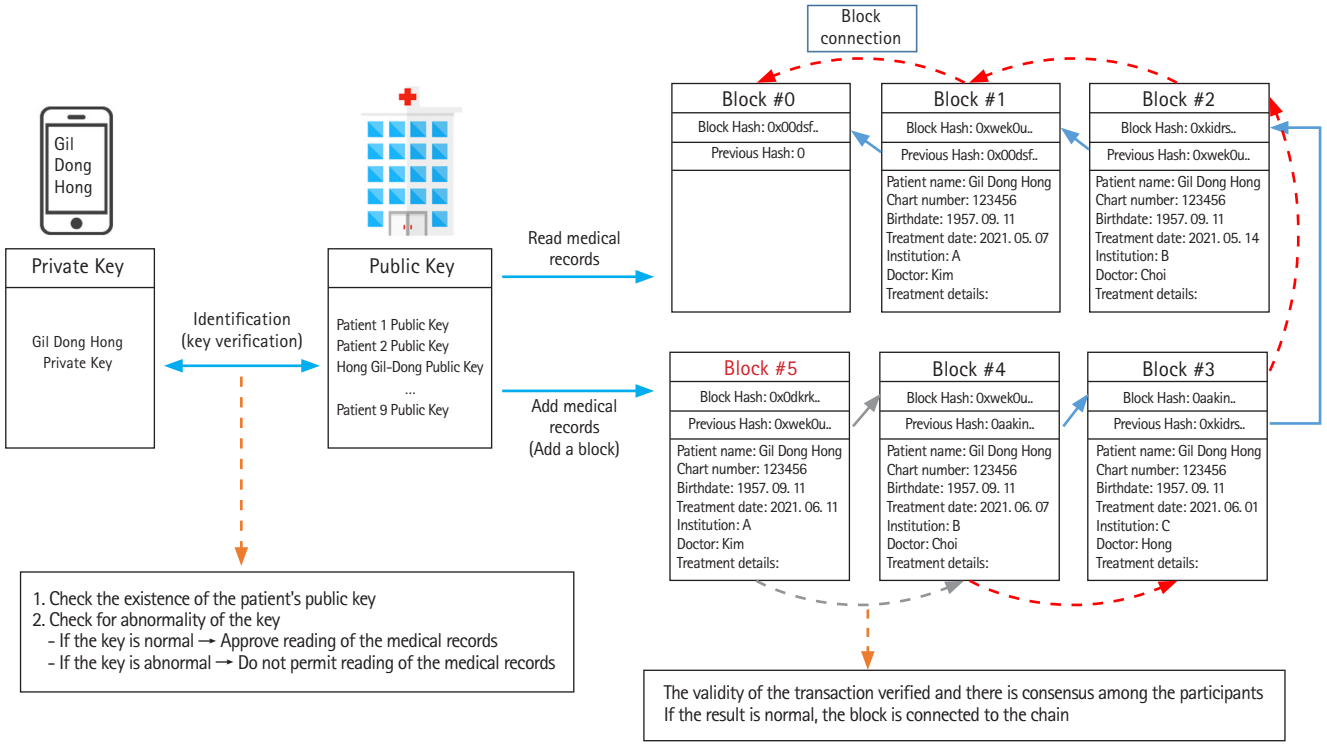

Fig. 2. Encryption process of the public key-based structure. After the consent to use and share personal medical information is provided, a unique pair of keys (private key, public key) is issued for the patient. An identity verification process is required to read or update medical records. The process is performed using the unique key pair assigned to the patient. Once the identity is verified normally, the patient's past medical records can be read, and new ones can be written. A new medical record is stored in a block, and if no abnormality is observed through validation verification, the new medical record is linked to the previous block and stored.

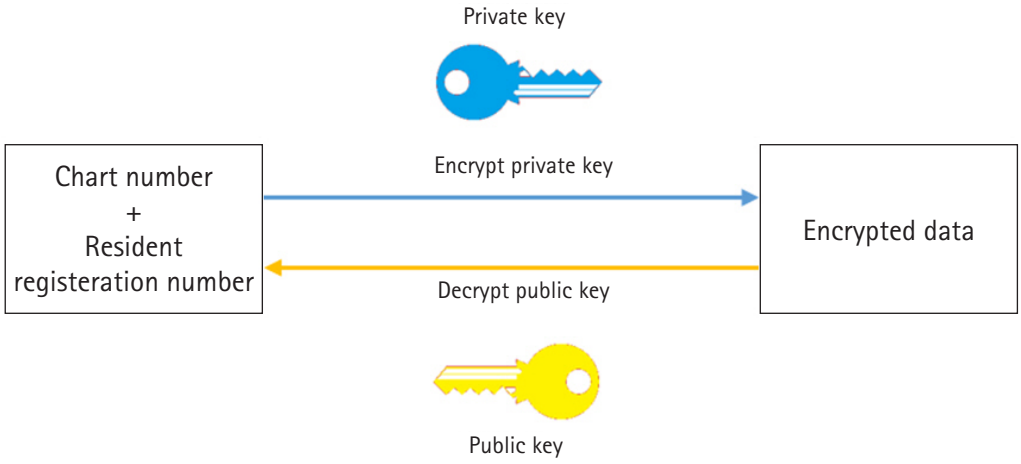

Fig. 3. Distribution and agreement process of medical information transaction. The verification and agreement process for medical information transaction is shown. The patient's identity verification process uses a public key-based structure that uses the Elliptic Curve Digital Signature Algorithm. The public key-based structure is a method of managing passwords with a pair of private and public keys, and facilitates the encryption of private keys using chart numbers or resident registration numbers. Data encrypted using the private key can be decrypted by only using the paired public key.

lidity is verified.

A text string file (.pem) is read and the private and public keys are extracted. The file is encrypted (signed) using the private key and decrypted using the public key.

Verification of the validity of private and public keys

```
// The private and public keys are read and initialized.
public void setFromFile(String privateKey, String publicKey)
throws Exception {
// A function to extract the private key from the certificate of a text
string format:
this.privateKey = new EC().readPrivateKeyFromPemFile(pri-
vateKey);
// A function to extract the public key from the certificate of a text
string format:
this.publicKey = new EC().readPublicKeyFromPemFile(pub-
licKey);
}

// The validity of the key is verified.
public static boolean isKeyVerify(String id, PrivateKey private-
Key, PublicKey publicKey) throws Exception{
boolean result;
Signature ecdsa;
Signature signature;
String text;
byte[] baText;
byte[] baSignature;
// Encryption (signature) using the private key:
ecdsa = Signature.getInstance("SHA1withECDSA");
ecdsa.initSign(privateKey);
text = id;
baText = text.getBytes("UTF-8");
// The data from the original source that are encrypted and signed
are output.
ecdsa.update(baText);
baSignature = ecdsa.sign();
// Decryption using the public key when verifying the data:
signature = Signature.getInstance("SHA1withECDSA");
signature.initVerify(publicKey);
signature.update(baText);
result = signature.verify(baSignature);
return result;
}
```

3. Reading and adding medical information

After successful identity verification, the medical institution can read the patient's past medical records and can update the record with new medical information (Fig. 3). The medical information is updated through the propagation of a transaction. Moreover, a medical record can be created, and the message by which it is created is expressed as a transaction. Transactions are propagated to participating medical institutions connected to the network. Each participating medical institution that receives a transaction updates its transaction information and propagates the transaction to another medical institution. When a medical institution receives a transaction, it needs a means to verify whether the transaction is correct. A digital or electronic signature is required for validity verification, and the original data (the patient's medical information) is therefore sent together with electronically signed data to verify that the transaction is correct and that the data has not been modified. Successfully verified transaction information is reflected in the hash value of the generated block.

Code: Validity test

A transaction object that records medical information is generated, and the validity of the transaction is verified.

Verification of the validity of transactions containing patients' medical information

```
transaction = new Transaction(key, patientsData.getPatientsDa-
ta());

// The transaction information to be propagated is created.
// The transaction information includes the patient's medical in-
formation, key information, electronically signed data, and trans-
action generation time.
public Transaction(Key key, String patientsData) throws Excep-
tion {
this.patientsData = patientsData
this.sender = key.getPublicKey();
this.timestamp = Util.getDate();
this.signature = key.sign(getData()); // Electronic signature of
original data
}

// The simple transaction information, excluding the signature
value, is returned.
public String getData() {
return new Util().getHash(sender.toString()) + timestamp + this.
patientsData
}

// The normality of the transaction is verified (a validity test).
public boolean verifyTransaction(Transaction transaction)
throws Exception {
Signature signature;
```

(Continued to the next page)

```
signature = Signature.getInstance("SHA1withECDSA");
byte[] baText = transaction.getData().getBytes("UTF-8");
signature.initVerify(transaction.getSender());
signature.update(baText);
return signature.verify(new BigInteger(transaction.getSignature(), 16).toByteArray());
}
```

The process for adding medical information to a patient's medical record is as follows: (1) The original data (medical information) is encrypted with the patient's own private key and electronically signed. (2) The original data and the electronically signed data are propagated to the participating medical institutions. (3) To verify whether the transaction is valid, the participating medical institutions decrypt it using the patient's public key. (4) The decrypted data and original data are compared to verify the integrity of the data and whether there is any manipulated data. (5) If the received transaction is determined to be valid, the transaction is updated in the blockchain, and the transaction is propagated to the medical institutions participating in the blockchain network.

4. Block connection

Whenever a transaction of medical information is performed, a block that contains the transaction information is generated and connected continuously to other blocks, and the information is stored in a distributed manner at the medical institutions participating in the network. Many blocks are closely interconnected through the hash values. A hash value is data that is converted to a special text string of a fixed length in which the original data cannot be distinguished when the hash goes through the hash function. The transaction information is reflected in the hash value of the newly generated block. When the internal data of a specific block in the blockchain changes, the hash value automatically changes, which also affects other blocks. In this way, a blockchain allows data tampering to be easily detected. In the blockchain, the hash value is used to add the corresponding block to the chain, and the hash value of the previous block is recorded in the current block. As a result, a connected list is created in the form of chain. Therefore, in order to hack a specific block, it is necessary to tamper with other blocks connected to the block of interest, making forgery exceedingly difficult.

Code: Generation of block objects

To create a block object, a verified transaction is added to the chain, and the transaction information is reflected in the hash value of the block. A new block hash is then generated using the previous block hash. The hash value of the previous block is saved in the newly generated block that follows it.

Generation of blockchain lists using hash values that reflect transaction information

```
block = new Block(block.getBlockID()+1, block.getBlockHash(), Util.getDate(), patientsData, new ArrayList < Transaction > ());

// A transaction is generated to add to the medical record of patient 2673123.
transaction = new Transaction(key, patientsData.getPatientsData());
block.addTransaction(transaction);

// The transaction information is reflected in the hash value of the block.// If the transaction information in a block is changed, the hash values of all subsequent blocks are also changed.
public String getBlockHash() {
// The block hash is created using the previous block hash.
return Util.getHash(getTransaction() + previousBlockHash);
}
// The SHA-256 hash value, which is returned as a text string, passes through the function.
// When the value of the text string changes, the hash value also changes.
// For the SHA-256 hash algorithm, the Avalanche Effect method is applied.
public static String getHash(String input) {
StringBuffer result = new StringBuffer();
try {
MessageDigest md = MessageDigest.getInstance("SHA-256");
md.update(input.getBytes());
byte bytes[] = md.digest();
for(int i = 0;i < bytes.lengthi++) {
result.append(Integer.toString((bytes[i] & 0xff) + 0x100, 16).substring(1));
}
} catch(Exception e) {
e.printStackTrace();
}
return result.toString();
}
```

SHA, secure hash algorithm.

The patient's medical information is stored in the generated block, and multiple blocks form a list that is connected through their hash values.

Blockchain list information

= =
Block number: 0
Created time: 2021-06-14 01:51:36.640
Previous hash: null
Block hash: 74234e98afe7498fb5daf1f36ac2d78acc339464f-950703b8c019892f982b90b
Medical record:
= =

A normal transaction was found.
= =
Block number: 1
Created time: 2021-06-14 01:51:39.661
Previous hash: 74234e98afe7498fb5daf1f36ac2d78acc339464f-950703b8c019892f982b90b
Block hash: 6345e8d4fe0b749dfe1862cbfd90817f38dd3692cd-2cd918be58e5becd540944
Medical record:
NAME: Gil Dong Hong
AGE: 50
GENDER: M
STROKE: Lt. hemiplegia d/t Rt. CR infarct
ONSET: Jan/01/2021
MEP: Jan/12/2021: Rt. ABP 20.6/5600, Lt. ABP NR; Rt. TA 19.5/2200, Lt. TA NR
SEP: Jan/12/2021 Rt. Median 19.0/24.2, Lt. Median NR; Rt. PT 38.2/45.0, Lt. PT NR
Evaluation data: Jan/10/2021
Bathel index: 30
MMSE: 24
GDS: 2
MVPT: 30
MFT: .30/8
Purdue: 16/NT
Grip Power: .50/6
Monofilament: 3.22/5.22
Two point discrimination: .4/6
Shoulder abductor: 1
Elbow flexor: 2
Finger flexor: 2
(Continued to)

Finger extensor: 1
Hip flexor: 2
Knee extensor: 2
Ankle D/F: 1
FAC: 1
Aphasia type: conduction aphasia
AQ: 55
LQ: 48
Light tough: .20/12
Kinesthetic: .20/12
MBC: 2
GCS: 15
= =

A normal transaction was found.
= =
Block number: 2
Created time: 2021-06-14 01:51:42.704
Previous hash: 6345e8d4fe0b749dfe1862cbfd90817f38d-d3692cd2cd918be58e5becd540944
Block hash: dbf72d6bf7143b6272308fb0708291c10733c0787553355753fb90e477113a7e
Medical record:
NAME: Gil Dong Hong
AGE: 50
GENDER: M
STROKE: Lt. hemiplegia d/t Rt. CR infarct
ONSET: Jan/01/2021
MEP: Jan/12/2021: Rt. ABP 20.6/5600, Lt. ABP NR; Rt. TA 19.5/2200, Lt. TA NR
SEP: Jan/12/2021 Rt. Median 19.0/24.2, Lt. Median NR; Rt. PT 38.2/45.0, Lt. PT NR
Evaluation data: Feb/10/2021
Bathel index: 52
MMSE: 27
GDS: 2
MVPT: 36
MFT: .30/10
Purdue: 16/NT
Grip Power: .50/8
Monofilament: 3.22/5.18
Two point discrimination: .4/6
Shoulder abductor: 2
Elbow flexor: 3
Finger flexor: 3
(Continued to the next page)

 https://doi.org/10.12701/yujm.2021.01368

Finger extensor: 1
Hip flexor: 3
Knee extensor: 3
Ankle D/F: 1
FAC: 2
Aphasia type: conduction aphasia
AQ: 58
LQ: 52
Light tough: .20/14
Kinesthetic: .20/14
MBC: 3
GCS: 15
= =

A normal transaction was found.
= =
Block number: 3
Created time: 2021-06-14 01:51:45.737
Previous hash: dbf72d6bf7143b6272308fb0708291c10733c0787553355753fb90e477113a7e
Block hash: f55e598438047feeafac137016eda953396244cff-fe148730499727203e72733
Medical record:
NAME: Gil Dong Hong
AGE: 50
GENDER: M
STROKE: Lt. hemiplegia d/t Rt. CR infarct
ONSET: Jan/01/2021
MEP: Jan/12/2021: Rt. ABP 20.6/5600, Lt. ABP NR; Rt. TA 19.5/2200, Lt. TA NR
SEP: Jan/12/2021 Rt. Median 19.0/24.2, Lt. Median NR; Rt. PT 38.2/45.0, Lt. PT NR
Evaluation data: Mar/13/2021
Bathel index: 58
MMSE: 28
GDS: 2
MVPT: 38
MFT: .30/12
Purdue: 16/NT
Grip Power: .50/8
Monofilament: 3.22/5.14
Two point discrimination: .4/6
Shoulder abductor: 3
Elbow flexor: 4
Finger flexor: 4
(Continued to)

Finger extensor: 2
Hip flexor: 3
Knee extensor: 3
Ankle D/F: 2

FAC: 3
Aphasia type: conduction aphasia
AQ: 58
LQ: 54
Light tough: .20/16
Kinesthetic: .20/16
MBC: 4
GCS: 15
= =

A normal transaction was found.
= =
Block number: 4
Created time: 2021-06-14 01:51:48.754
Previous hash: f55e598438047feeafac137016eda953396244cff-fe148730499727203e72733
Block hash: 5fdfbc0a7d30f454dfc24975805e353ca5912b4d-81c9875447e6a99644650a8f
Medical record:
NAME: Gil Dong Hong
AGE: 50
GENDER: M
STROKE: Lt. hemiplegia d/t Rt. CR infarct
ONSET: Jan/01/2021
MEP: Jan/12/2021: Rt. ABP 20.6/5600, Lt. ABP NR; Rt. TA 19.5/2200, Lt. TA NR
SEP: Jan/12/2021 Rt. Median 19.0/24.2, Lt. Median NR; Rt. PT 38.2/45.0, Lt. PT NR
Evaluation data: May/01/2021
Bathel index: 60
MMSE: 28
GDS: 2
MVPT: 40
MFT: .30/12
Purdue: 16/NT
Grip Power: .50/8
Monofilament: 3.22/5.14
Two point discrimination: .4/6
Shoulder abductor: 3
Elbow flexor: 4
(Continued to the next page)

```
Finger flexor: 4
Finger extensor: 2
Hip flexor: 3
Knee extensor: 3
Ankle D/F: 2
FAC: 4
Aphasia type: conduction aphasia
AQ: 58
LQ: 56
Light tough: .20/16
Kinesthetic: .20/16
MBC: 4
GCS: 15
= = = = = = = = = = = = = = = = = = = = = = = = = = = = =
```

MEP, motor evoked potential; ABP, abductor pollicis brevis; Rt, right; Lt, left; TA, tibialis anterior; PT, posterior tibial; NR, no response; SEP, sensory evoked potential; MMSE, mini-mental state examination; GDS, global deterioration scale; MVPT, motor-free visual perception test; MFT, manual function test; NT, not testable; D/F, dorsiflexor; FAC, functional ambulatory category; AQ, aphasia quotient; LQ, language quotient; MBC, modified Brunnstrom Classification; GCS, Glasgow Coma Scale.

Discussion

In this study, we created a simple blockchain for the purpose of allowing hospitals to exchange patient information on a network in a way that makes hacking practically impossible. The proposed information sharing method only allows the medical staff of a hospital to see a patient's information stored on the network in the form of a blockchain if there is a private key stored on the patient's smartphone. This method circumvents the inconvenience of the current system in which patients must print out their medical records and deliver them to the new hospital when being transferred. Clinicians may be concerned that due to its decentralized nature, if blockchain is used in the medical field, patients will become the guardians of their medical information. Nevertheless, in the proposed system, the patients do not directly possess their own medical information. Hence, we expect that the aversion of doctors to information sharing via blockchain will be small.

This study only included the information that is required by clinicians to treat stroke rehabilitation patients in the blockchain. The information was based on the paper by Kim et al. [7] published in 2021. Through a Delphi study, they collected the essential medical information of stroke rehabilitation patients when transferred to another hospital from 31 physiatrists. They found that the degree of muscle strength at major joints; a brief cognitive function test; and hand, language, and sensory function were essential information for treatment. We, therefore, added this essential information of stroke patients to the blockchain, and the information was stored.

This is the first study to demonstrate the possibility of using blockchain for the storage and delivery of the patient information of stroke patients by storing the information in a blockchain. The code that we wrote may not be suitable for direct implementation in the medical field, but it can serve as a foundation for researchers to create a blockchain system that can be actually used in the field based on future research results.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

The present study was supported by a National Research Foundation of Korea grant funded by the Korean government (grant no. NRF-2019M3E5D1A02068106).

Author contributions

Conceptualization, formal analysis, investigation, supervision, Writing-original draft, wiring-review & editing: CMC.

ORCID

Min Cheol Chang, https://orcid.org/0000-0002-7629-7213

References

1. Chang MC, Hau YS, Park JC, Lee JM. The application of blockchain technology in stroke rehabilitation. Am J Phys Med Rehabil 2019;98:e74.
2. Kuo TT, Kim HE, Ohno-Machado L. Blockchain distributed ledger technologies for biomedical and health care applications. J Am Med Inform Assoc 2017;24:1211–20.
3. Chang MC, Hsiao MY, Boudier-Revéret M. Blockchain technology: efficiently managing medical information in the pain management field. Pain Med 2020;21:1512–3.
4. Dutta P, Choi TM, Somani S, Butala R. Blockchain technology in supply chain operations: applications, challenges and research opportunities. Transp Res E Logist Transp Rev 2020; 142:102067.
5. Karandikar N, Chakravorty A, Rong C. Blockchain based transaction system with fungible and non-fungible tokens for a community-based energy infrastructure. Sensors (Basel) 2021;

21:3822.
6. Fang HS, Tan TH, Tan YF, Tan CJM. Blockchain personal health records: systematic review. J Med Internet Res 2021;23:e25094.
7. Kim JK, Hau YS, Kwak S, Chang MC. Essential medical information for stroke patients undergoing interhospital transfer: a Delphi study. Am J Phys Med Rehabil 2021;100:354–8.

Original article

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):108-115
https://doi.org/10.12701/yujm.2021.01123

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Clinical performance of FractionLab in patient-specific quality assurance for intensity-modulated radiotherapy : a retrospective study

Se An Oh[1], Sung Yeop Kim[2], Jaehyeon Park[1], Jae Won Park[1], Ji Woon Yea[1]

[1]Department of Radiation Oncology, Yeungnam University College of Medicine, Daegu, Korea
[2]Department of Physics, Yeungnam University, Gyeongsan, Korea

Background: This study was aimed at comparing and analyzing the results of FractionLab (Varian/Mobius Medical System) with those of portal dosimetry that uses an electronic portal imaging device. Portal dosimetry is extensively used for patient-specific quality assurance (QA) in intensity-modulated radiotherapy (IMRT).
Methods: The study includes 29 patients who underwent IMRT on a Novalis-Tx linear accelerator (Varian Medical System and BrainLAB) between June 2019 and March 2021. We analyzed the multileaf collimator DynaLog files generated after portal dosimetry to evaluate the same condition using FractionLab. The results of the recently launched FractionLab at various gamma indices (0.1%/0.1 mm–1%/1 mm) are analyzed and compared with those of portal dosimetry (3%/3 mm).
Results: The average gamma passing rates of portal dosimetry (3%/3 mm) and FractionLab are 98.1% (95.5%–100%) and 97.5% (92.3%–99.7%) at 0.6%/0.6 mm, respectively. The results of portal dosimetry (3%/3 mm) are statistically comparable with the QA results of FractionLab (0.6%/0.6 mm–0.9%/0.9 mm).
Conclusion: This paper presents the clinical performance of FractionLab by the comparison of the QA results of FractionLab using portal dosimetry with various gamma indexes when performing patient-specific QA in IMRT treatment. Further, the appropriate gamma index when performing patient-specific QA with FractionLab is provided.

Keywords: Electronic portal imaging device; FractionLab; Gamma passing rate; Intensity-modulated radiotherapy; Patient-specific quality assurance

Introduction

Intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), which deliver the desired radiation dose to the targeted tumors with minimal radiation to the surrounding normal tissue, are extensively used in radiotherapy. IMRT technology increases the daily radiation dose (dose per fraction) based on these technical advantages and contributes significantly to patient convenience by enhancing the radiation treatment effect and reducing the radiation treatment period [1-8]. In particular, Huh et al. [9] reported that the number of IMRT cases increased significantly by a factor of approximately 18 from 2011 to 2018 owing to the expansion of the national health insurance coverage in Korea.

IMRT modulates the photon-beam intensity by changing the position of the multileaf collimator (MLC) [10], thereby deliver-

Received: May 12, 2021 • **Revised:** June 22, 2021 • **Accepted:** August 13, 2021
Corresponding author: Ji Woon Yea, MD, PhD
Department of Radiation Oncology, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3371 • Fax: +82-53-624-3599 • E-mail: yjw1160@ynu.ac.kr

ing a nonuniform fluence from any given position of the patient's treatment beam and optimizing the dose distribution [11]. However, the calculation of the small or irregular fields frequently used in IMRT has been reported as inaccurate; even with state-of-the-art dose calculation algorithms, the calculated dose distribution and the dose distribution delivered to the patient may differ [10]. Therefore, for all patients undergoing IMRT treatment, patient-specific quality assurance (QA) must be performed prior to radiotherapy [12]. Patient-specific QA is generally analyzed using various tools, such as ion chambers, thermoluminescent dosimeters (TLDs), film dosimetry, electronic portal imaging devices (EPIDs), and two-dimensional (2D) arrays. In particular, the gamma index analysis method, which compares and analyzes the calculated and measured doses, is the most used for patient-specific QA in IMRT treatment. In IMRT treatment, although the values of acceptable dose difference (DD) and distance-to-agreement (DTA) are not clearly defined, the clinically well-accepted values are 3% and 3 mm, respectively [10-17]. Our institution used these same values; as the passing criterion, such as DD or DTA increases, the passing gamma value will increase.

Recently, FractionLab (Varian/Mobius Medical System, Houston, TX, USA), presented a gamma index analysis of the planned and delivered fluences based on MLC log files by using a phantom-free method. FractionLab automatically analyzes the machine log files that can be generated by a medical linear accelerator. In addition, the log files can be analyzed in bulk, and several machine performance metrics, such as the MLC positioning errors, beam shutoff speed, and planned/delivered gamma agreement, can be assessed [18]. Nevertheless, the clinical performance of FractionLab has not yet been reported.

This study compared the clinical performance of FractionLab with portal dosimetry, one of the most commonly used tools for patient-specific QA in IMRT treatment. Furthermore, we attempted to determine an appropriate gamma index when performing patient-specific QA by using FractionLab.

Methods

Ethical statements: The study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2022-03-011), which waived the need for informed consent due to the retrospective design of the study.

1. Study design and participants

This study is a retrospective data analysis involving 29 patients who underwent IMRT on Novalis-Tx (Varian Medical System, Palo Alto, CA and BrainLAB, Feldkirchen, Germany) linear accelerators from June 2019 to March 2021. Table 1 lists the characteristics of these patients. The treated area distribution, included in the study, shows the brain as the most commonly treated area (16 patients, 55.2%), followed by the pelvis (six patients, 20.7%), lung (four patients, 13.8%), and head and neck (three patients, 10.3%).

2. Treatment planning and delivery techniques

All the radiation treatments were performed using a fixed-gantry method, and the radiation was delivered using a sliding window method, in which the MLC was continuously moved during radiation exposure.

3. Electronic portal imaging device

Portal dosimetry (Varian Medical System) was performed for the fluences measured using an amorphous silicon (aS1000) EPID attached to the linear accelerator [10,19]. The EPID has a matrix of 1,024 × 768 pixels and detects a size of 40 × 30 cm^2 on the surface [20]. Fig. 1 shows the patient-specific QA method with the EPID in the portal dosimetry for IMRT. Portal dosimetry is extensively applied for patient-specific QA in complex radiotherapy such as IMRT and VMAT. Because portal dosimetry does not require a phantom setup, the QA time can be reduced; thus, it is widely used routinely in clinical practice. Although portal dosimetry has high resolution and reduces the QA time, it cannot verify patient dose calculation algorithms such as pencil beam convolution, anisotropic analytical algorithm, and Acuros XB algorithm. Portal dosimetry is calculated from the fluence map rather than the dose map calculation.

Fig. 2 illustrates patient-specific QA using portal dosimetry. Fig. 2A shows the portal dose image predicted by the portal dose

Table 1. Characteristics of the studied patients treated using intensity-modulated radiotherapy techniques on the Novalis-Tx

Characteristic	Data
No. of patients	29
Age (yr)	66 (39–87)
Sex	
Female	5 (17.2)
Male	24 (82.8)
Treated region	
Brain	16 (55.2)
Head and neck	3 (10.3)
Lung	4 (13.8)
Pelvis	6 (20.7)

Values are presented as number only, median (range), or number (%).
Novalis-Tx, Varian Medical System, Palo Alto, CA, USA.

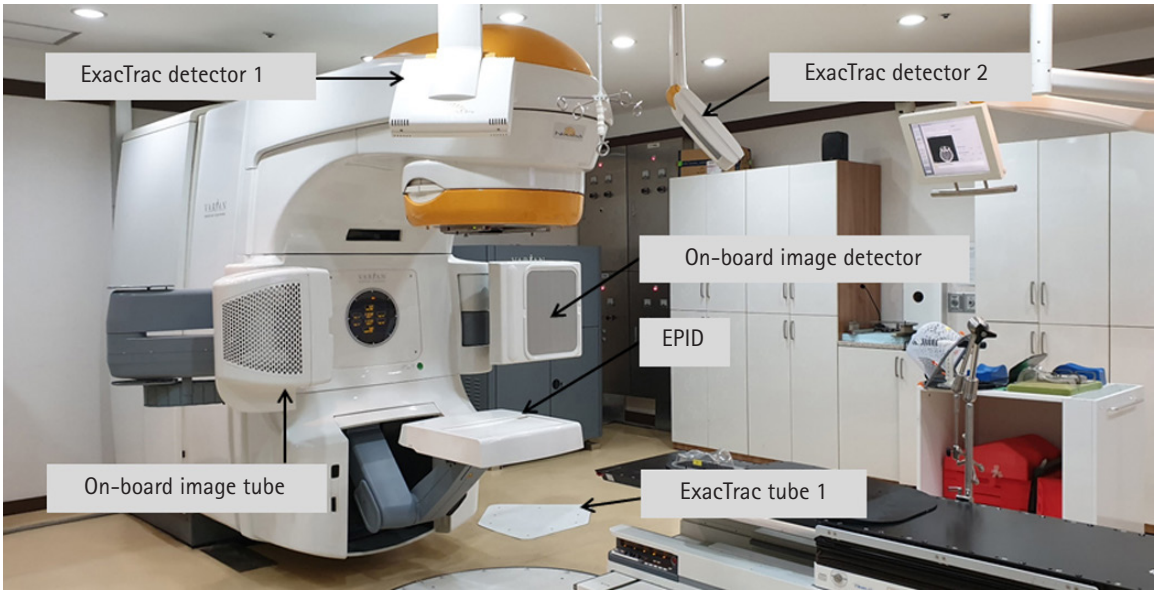

Fig. 1. Patient-specific quality assurance with amorphous silicon (aS1000) electronic portal imaging device (EPID)-based portal dosimetry.

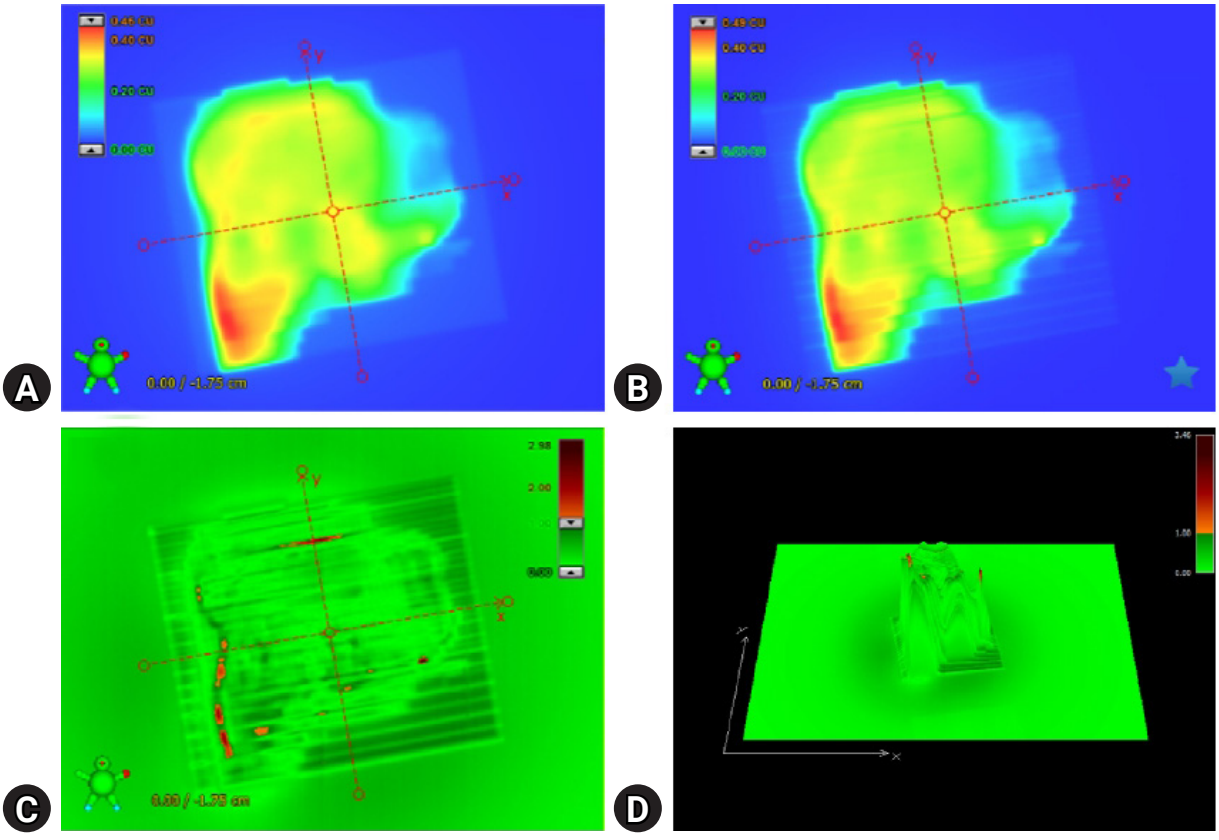

Fig. 2. Example of patient-specific quality assurance with portal dosimetry. (A) Portal dose image predicted by the portal dose image prediction (PDIP) algorithm, a dedicated two-dimensional algorithm for dose prediction. (B) Portal dose image measured by the electronic portal imaging device. (C) Gamma (3%/3 mm) evaluation between the predicted and measured portal dose images. (D) Three-dimensional gamma (3%/3 mm) image on the portal dose image.

 https://doi.org/10.12701/yujm.2021.01123

image prediction algorithm, which is a 2D algorithm dedicated to dose prediction, and Fig. 2B shows the image measured using the EPID. Fig. 2C depicts the gamma (3%/3 mm) evaluation between the predicted and measured portal dose images, and Fig. 2D depicts the 3D gamma (3%/3 mm) image of the portal dose image.

4. FractionLab

DoseLab (Varian Medical Systems) consists of three separate products: DoseLab, TG-142, and FractionLab. The FractionLab software automatically analyzes the machine log files that can be automatically generated by linear accelerators, as shown in Fig. 3.

Fig. 4 illustrates patient-specific QA using FractionLab. Fig. 4A and 4B depict the planned fluence image and the fluence image delivered by the log files, and Fig. 4C shows the gamma (0.6%/0.6 mm) evaluation between the planned and delivered fluence images.

FractionLab performs gamma evaluation between the automatically calculated 2D fluence and the 2D fluence generated using the log files after irradiation. The machine log files include the delivered MLC position information as a function of the fractional dose, which is used by FractionLab to create fluence maps magnified on the isocenter plane. These fluence maps are generated at a fixed resolution of 0.5 mm per pixel [18]. Two files ('A' bank and 'B' bank) were created for the machine log files of a field. FractionLab can evaluate several aspects of the machine performance such as the MLC position error, beam cutoff rate, and plan/delivery gamma agreement. DynaLog files were generated for the Varian Clinic and Varian Trilogy accelerators, and trajectory log files were generated for the Varian TrueBeam accelerators. The DynaLog files were used in this study. The general parameter specifications are as follows: sampling time = 0.05 sec, MLC position = 0.01 mm, jaw position = 0.1 cm, and gantry angle = 0.1°; the couch angle is not reflected in the log files [18].

5. Analysis of the gamma index between the electronic portal imaging device and FractionLab

Portal dosimetry was performed using a 3% DD and 3-mm DTA, which are commonly used in clinical practice for gamma evaluation. We analyzed the MLC DynaLog files generated after portal dosimetry to evaluate the same condition using FractionLab. We evaluated the gamma value using FractionLab, by varying the DD/DTA values from 0.1%/0.1 mm to 1%/1 mm.

6. Statistical analyses

We conducted a paired *t*-test on the portal dosimetry and Fraction-

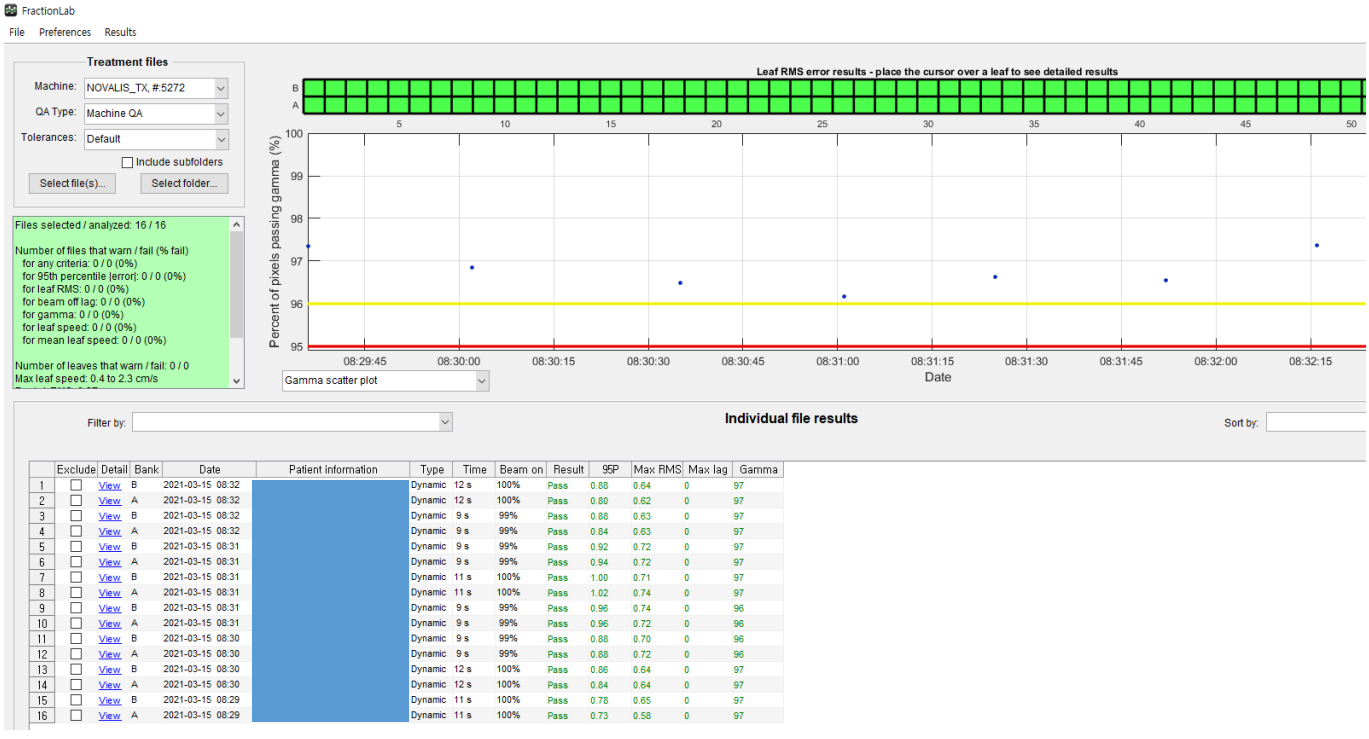

Fig. 3. Image of the gamma scatter plot by field using multileaf collimator (MLC) log files (.dlg) and FractionLab (Varian/Mobius Medical System, Houston, TX, USA), generated after the radiotherapy treatment of one of the patients included in the study; one field creates two dlg files ('A' and 'B' banks).

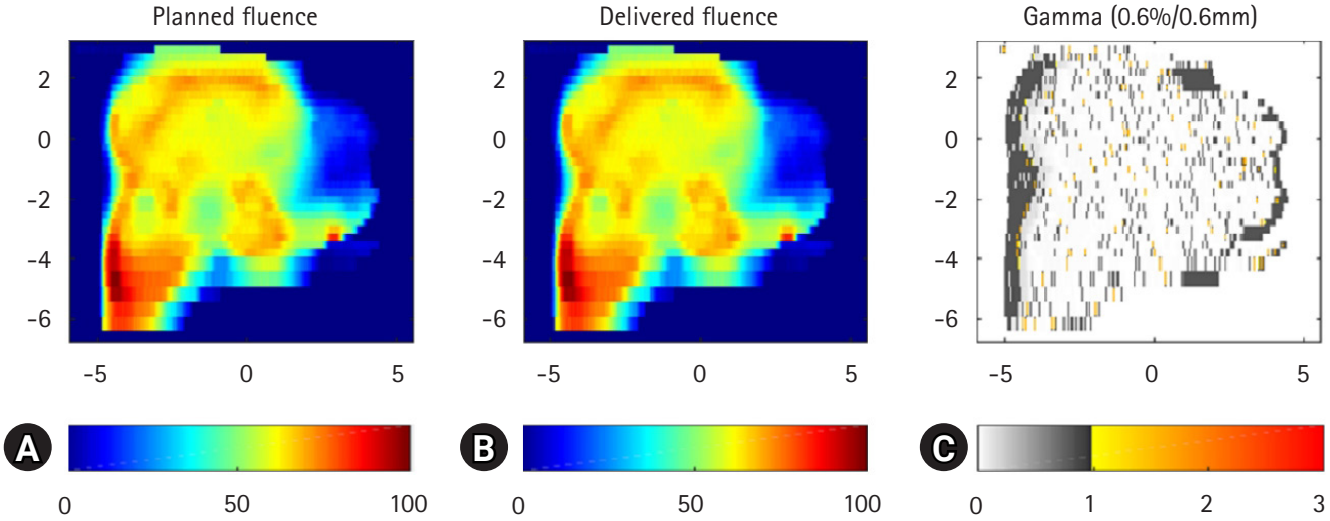

Fig. 4. Example of patient-specific quality assurance with FractionLab (Varian/Mobius Medical System, Houston, TX, USA). (A) Planned fluence image, (B) Fluence image delivered by the log files, and (C) gamma (0.6%/0.6 mm) evaluation between the planned and delivered fluence images.

Lab QA results to determine an appropriate gamma index when using FractionLab-based patient-specific QA, as a 3%/3 mm gamma index was considered when performing QA using portal dosimetry. Statistical analysis was performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The gamma passing rates of portal dosimetry (3%/3 mm) and FractionLab at various gamma criteria (0.1%/0.1–1%/1 mm) were analyzed, where $p \leq 0.05$ was considered statistically significant.

Results

The gamma passing rates of portal dosimetry (3%/3 mm) and FractionLab at various gamma criteria (0.1%/0.1–1%/1 mm) for IMRT are depicted in Table 2 and Fig. 5.

The average gamma passing rate of portal dosimetry (3%/3 mm) is 98.1% (95.5%–100%). In FractionLab, gamma evaluation was performed from 0.1%/0.1 mm to 1%/1 mm in steps of 0.1%/0.1 mm. The average gamma passing rates (range) of FractionLab are 69.7% (37.7%–77.3%), 70.6% (40.1%–77.6%), 72.4% (48.3%–86.3%), 74.5% (54.5%–94.4%), 96.4% (90.4%– 99.6%), 97.5% (92.3%–99.7%), 97.8% (92.5%–99.9%), 98.1% (92.8%–99.9%), 98.5% (93.0%–100%), and 99.5% (98.1%–100%).

Therefore, it can be said that the paired *t*-test results for the average value of portal dosimetry (3%/3 mm) and FractionLab exhibit statistically significant differences for gamma indices below 0.6%/0.6 mm and 1%/1 mm.

Table 2. Gamma passing rates of portal dosimetry (3%/3 mm) and FractionLab for various gamma criteria (0.1%/0.1–1%/1 mm) in intensity modulated radiotherapy

FractionLab		Portal dosimetry (3%/3 mm)	*p*-value[b]
Gamma criteria (%/mm)	Gamma passing rates[a]	Gamma passing rates[a]	
0.1/0.1	69.7 (37.7–77.3)	98.1 (95.5–100)	<0.001
0.2/0.2	70.6 (40.1–77.6)	98.1 (95.5–100)	<0.001
0.3/0.3	72.4 (48.3–86.3)	98.1 (95.5–100)	<0.001
0.4/0.4	74.5 (54.5–94.4)	98.1 (95.5–100)	0.001
0.5/0.5	96.4 (90.4–99.6)	98.1 (95.5–100)	0.001
0.6/0.6	97.5 (92.3–99.7)	98.1 (95.5–100)	0.127
0.7/0.7	97.8 (92.5–99.9)	98.1 (95.5–100)	0.519
0.8/0.8	98.1 (92.8–99.9)	98.1 (95.5–100)	0.965
0.9/0.9	98.5 (93.0–100.0)	98.1 (95.5–100)	0.306
1.0/1.0	99.5 (98.1–100.0)	98.1 (95.5–100)	<0.001

[a]Median (range). [b]By paired *t*-test.
FractionLab, Varian/Mobius Medical System, Houston, TX, USA.

Discussion

Complex and sophisticated radiotherapy technologies, such as IMRT and VMAT, which deliver the desired radiation dose to the targeted tumors with minimum dosage to the surrounding normal organs, have a complex dose distribution and steep dose gradient. Therefore, patient-specific QA is crucial in radiotherapy [11-13,15,16].

Recently, various IMRT QA methods have been proposed for patient-specific QA [10,11]. In this study, the mean values of por-

 https://doi.org/10.12701/yujm.2021.01123

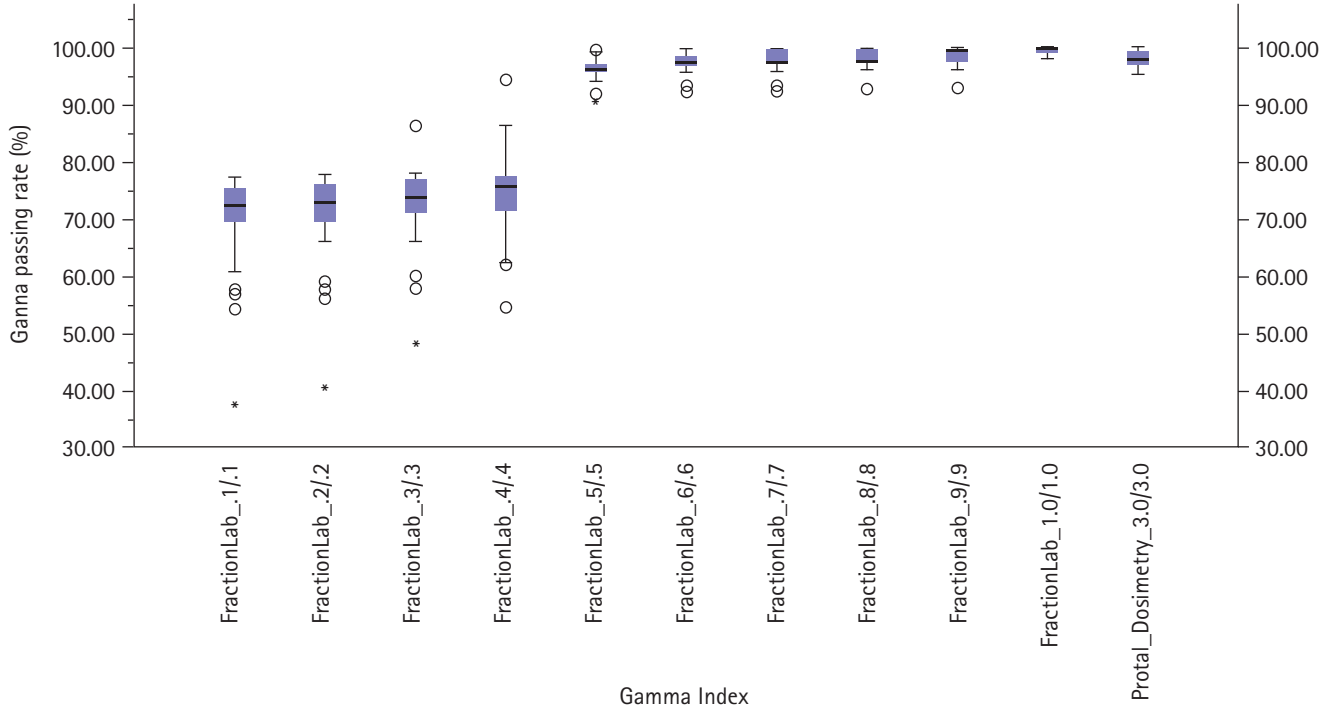

Fig. 5. Gamma passing rates of portal dosimetry (3%/3 mm) and FractionLab (Varian/Mobius Medical System, Houston, TX, USA) at various gamma indices (0.1%/0.1 mm–1%/1 mm).

tal dosimetry (3%/3 mm) and FractionLab (included in DoseLab) at various gamma indices were compared, and the statistical differences were analyzed through a paired *t*-test.

Kim et al. [10] investigated the characteristics of portal dosimetry in comparison with the MapCHECK2 (Sun Nuclear Corporation, Melbourne, FL, USA) measurement with respect to 65 treatment plans, including IMRT and VMAT, for various linear accelerator machines (VitalBeam, Trilogy, Clinac 21EXS, and Clinac Ix [Varian Medical System, Palo Alto, CA, USA]). When using portal dosimetry for patient-specific QA in IMRT treatment, most evaluation criteria for the gamma index include a gamma criterion of 3%/3 mm and gamma values of ≥ 95% as pass criteria. Therefore, we analyzed the QA results by using the 3%/3 mm gamma criteria of portal dosimetry and logfiles generated by irradiation in portal dosimetry using FractionLab with various gamma indices. We tried to find an appropriate gamma index when performing patient-specific QA with FractionLab using the QA results of portal dosimetry. The results showed that performing gamma index in the range of 0.6%/0.6 mm and 0.9%/0.9 mm is appropriate if FractionLab is used for patient-specific QA in IMRT.

Patient-specific QA has been conventionally performed using a phantom-based system with various QA tools such as ion chambers, TLDs, film dosimetry, EPID, and 2D arrays. However, the use of such a phantom-based QA is time-consuming and the dose per fraction delivered cannot be tracked. In addition, this method is incapable of determining the root cause of failures. Moreover, the conventional method ignores patient-specific anatomical variations. In comparison, a logfiles-based QA system, such as Mobius3D (Varian Medical System) and ArcCHECK (Sun Nuclear), will enable automation, tracking of heterogeneous anatomical dose, and allow for root-cause analysis [21].

As no clinical data on patient-specific QA using FractionLab are currently available, the clinical results of this study can be useful for medical physicists in radiation oncology.

However, this study has some limitations. First, we only analyzed the clinical performance of the two systems by using the gamma analysis method based on portal dosimetry and FractionLab, and did not provide a detailed analysis of the algorithms of the two systems. Second, this study included only fixed-gantry IMRT patients. More complex radiotherapy, such as VMAT, may produce different results. In the future, it would be necessary to compare the existing patient-specific QA methods for treatments such as VMAT and various linear accelerators.

This study showed the clinical performance of FractionLab by comparing its QA results using portal dosimetry and various gamma indexes with the results of patient-specific QA in IMRT treatment. The proposed method can present the appropriate gamma index when performing patient-specific QA with FractionLab. In

patient-specific QA of IMRT treatment, the QA result using a gamma index of 3%/3 mm using portal dosimetry is considered interchangeable with the QA result obtained using a gamma index in the range of 0.6%/0.6 mm and 0.9%/0.9 mm of FractionLab.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2021R1G1A1003209).

Author contributions

Conceptualization: SAO, SYK, JP, JWP, JWY; Data curation, Formal analysis: SYK, JWY; Funding acquisition: SAO; Methodology: SYK, JP, JWP; Investigation: SAO, SYK; Validation: JP, JWP; Project administration, Software, Supervision: JWY; Writing - original draft: SAO; Writing - review & editing: SAO, JP, JWP, JWY.

ORCID

Se An Oh, https://orcid.org/0000-0002-8835-2814
Sung Yeop Kim, https://orcid.org/0000-0002-2921-6126
Jaehyeon Park, https://orcid.org/0000-0003-2546-4808
Jae Won Park, https://orcid.org/0000-0003-1100-5301
Ji Woon Yea, https://orcid.org/0000-0002-7699-342X

References

1. Dai X, Zhao Y, Liang Z, Dassarath M, Wang L, Jin L, et al. Volumetric-modulated arc therapy for oropharyngeal carcinoma: a dosimetric and delivery efficiency comparison with static-field IMRT. Phys Med 2015;31:54–9.
2. Ali M, Babaiah M, Madhusudhan N, George G. Comparative dosimetric analysis of IMRT and VMAT (RapidArc) in brain, head and neck, breast and prostate malignancies. Int J Cancer Ther Oncol 2015;3:03019.
3. Mani KR, Upadhayay S, Das KJ. Influence of jaw tracking in intensity-modulated and volumetric-modulated arc radiotherapy for head and neck cancers: a dosimetric study. Radiat Oncol J 2017;35:90–100.
4. Liu X, Huang E, Wang Y, He Y, Luo H, Zhong M, et al. Dosimetric comparison of helical tomotherapy, VMAT, fixed-field IMRT and 3D-conformal radiotherapy for stage I-II nasal natural killer T-cell lymphoma. Radiat Oncol 2017;12:76.
5. Deng X, Han C, Chen S, Xie C, Yi J, Zhou Y, et al. Dosimetric benefits of intensity-modulated radiotherapy and volumetric-modulated arc therapy in the treatment of postoperative cervical cancer patients. J Appl Clin Med Phys 2017;18:25–31.
6. Mellon EA, Javedan K, Strom TJ, Moros EG, Biagioli MC, Fernandez DC, et al. A dosimetric comparison of volumetric modulated arc therapy with step-and-shoot intensity modulated radiation therapy for prostate cancer. Pract Radiat Oncol 2015;5:11–5.
7. Oh SA, Yea JW, Park JW, Park J. Use of a head-tilting baseplate during volumetric-modulated arc therapy (VMAT) to better protect organs at risk in hippocampal sparing whole brain radiotherapy (HS-WBRT). PLoS One 2020;15:e0232430.
8. Oh SA, Kang MK, Kim SK, Yea JW. Comparison of IMRT and VMAT techniques in spine stereotactic radiosurgery with international spine radiosurgery consortium consensus guidelines. Prog Med Phys 2013;24:145–53.
9. Huh SJ, Park W, Choi DH. Recent trends in intensity-modulated radiation therapy use in Korea. Radiat Oncol J 2019;37:249–53.
10. Kim JI, Choi CH, Park SY, An H, Wu HG, Park JM. Gamma evaluation with portal dosimetry for volumetric modulated arc therapy and intensity-modulated radiation therapy. Prog Med Phys 2017;28:61–6.
11. Yea JW, Park JW, Kim SK, Kim DY, Kim JG, Seo CY, et al. Feasibility of a 3D-printed anthropomorphic patient-specific head phantom for patient-specific quality assurance of intensity-modulated radiotherapy. PLoS One 2017;12:e0181560.
12. Ezzell GA, Burmeister JW, Dogan N, LoSasso TJ, Mechalakos JG, Mihailidis D, et al. IMRT commissioning: multiple institution planning and dosimetry comparisons, a report from AAPM Task Group 119. Med Phys 2009;36:5359–73.
13. Oh SA, Yea JW, Lee R, Park HB, Kim SK. Dosimetric verifications of the output factors in the small field less than 3 cm2 using the Gafchromic EBT2 films and the various detectors. Prog Med Phys 2014;25:218–24.
14. Oh SA, Kang MK, Yea JW, Kim SH, Kim KH, Kim SK. Comparison of intensity modulated radiation therapy dose calculations with a PBC and AAA algorithms in the lung cancer. Korean J Med Phys 2012;23:48–53.
15. Olaciregui-Ruiz I, Vivas-Maiques B, Kaas J, Perik T, Wittkamper F, Mijnheer B, et al. Transit and non-transit 3D EPID dosimetry versus detector arrays for patient specific QA. J Appl Clin Med Phys 2019;20:79–90.
16. Han B, Ding A, Lu M, Xing L. Pixel response-based EPID do-

simetry for patient specific QA. J Appl Clin Med Phys 2017;18:9–17.
17. Defoor DL, Stathakis S, Roring JE, Kirby NA, Mavroidis P, Obeidat M, et al. Investigation of error detection capabilities of phantom, EPID and MLC log file based IMRT QA methods. J Appl Clin Med Phys 2017;18:172–9.
18. Varian Medical Systems. DoseLab user guide - version 7.0 [Internet]. Houston, TX: Varian Medical Systems; 2018 [cited 2021 May 6]. https://www.myvarian.com/s/productdocumentation?lang=en.
19. Kim YL, Chung JB, Kim JS, Lee JW, Choi KS. Comparison of the performance between portal dosimetry and a commercial two-dimensional array system on pretreatment quality assurance for volumetric-modulated arc and intensity-modulated radiation therapy. J Korean Phys Soc 2014;64:1207–12.
20. Krishna Murthy K. Patient-specific quality assurance of RapidArc treatments: portal prediction dosimetry compared with phantom studies. Biomed Imaging Interv J 2012;8:e28.
21. Stanhope CW, Drake DG, Liang J, Alber M, Söhn M, Habib C, et al. Evaluation of machine log files/MC-based treatment planning and delivery QA as compared to ArcCHECK QA. Med Phys 2018;45:2864–74.

Original article

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):116-123
https://doi.org/10.12701/yujm.2021.01319

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

User perception of medical service robots in hospital wards: a cross-sectional study

Jung Hwan Lee, Jae Meen Lee, Jaehyun Hwang, Joo Young Park, Mijeong Kim, Dong Hwan Kim, Jae Il Lee, Kyoung Hyup Nam, In Ho Han

Department of Neurosurgery and Medical Research Institute, Pusan National University Hospital, Busan, Korea

Background: Recently, there have been various developments in medical service robots (MSRs). However, few studies have examined the perceptions of those who use it. The purpose of this study is to identify user perceptions of MSRs.
Methods: We conducted a survey of 320 patients, doctors, and nurses. The contents of the survey were organized as follows: external appearances, perceptions, expected utilization, possible safety accidents, and awareness of their responsibilities. Statistical analyses were performed using *t*-test, chi-square test, and analysis of variance.
Results: The most preferred appearance was the animal type, with a screen. The overall average score of positive questions was 3.64±0.98 of 5 points and that of negative questions was 3.24±0.99. Thus, the results revealed that the participants had positive perceptions of MSR. The overall average of all expected utilization was 4.05±0.84. The most expected utilization was to guide hospital facilities. The most worrisome accident was exposure to personal information. Moreover, participants thought that the overall responsibility of the robot user (hospital) was greater than that of the robot manufacturer in the case of safety accidents.
Conclusion: The perceptions of MSRs used in hospital wards were positive, and the overall expected utilization was high. It is necessary to recognize safety accidents for such robots, and sufficient attention is required when developing and manufacturing robots.

Keywords: Hospitals; Perception; Robotics; Surveys and questionnaires

Introduction

The fourth industrial revolution, represented by big data, the Internet of Things, artificial intelligence, and robotics, is underway worldwide [1]. Numerous studies have examined the development of various robots to replace human tasks [2]. There have also been many studies related to robots in the medical field. These include surgical robots, rehabilitation robots, nursing assistant robots, and hospital logistics robots [3]. Among these robots, surgical robots have been actively used [4]. However, with the exception of some telemedicine robots, there are few cases in which robots can care or monitor the patient in a real hospital. Nevertheless, advances in robot technology continue to increase interest in medical service robots (MSRs) that can replace or reduce medical and nursing work in hospitals. However, actual medical service development should begin with a sufficient understanding of the actual needs in the medical field and possible problems. Although there have been perception surveys for some nurses so far, they have been limited to care robots [3,5]. Those who use medical robots in hospital wards include nurses, patients who receive medical services, and doctors. The perceptions of MSR users are also very important, but there are no multi-dimensional perception surveys

Received: July 19, 2021 • **Revised:** August 8, 2021 • **Accepted:** August 21, 2021
Corresponding author: In Ho Han, MD, PhD
Department of Neurosurgery, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea
Tel: +82-51-240-7257 • Fax: +82-51-244-0282 • E-mail: farlateral@pusan.ac.kr

on MSR that include doctors and patients.

Therefore, the purpose of this study was to investigate user perceptions, needs, and possible problems for MSRs before developing robots that assist or replace treatment and nursing for patients in hospital wards. It also aims to provide important information for robot developers who wish to develop medical robots by evaluating user perceptions.

Methods

Ethical statements: With the approval of the Institutional Review Board (IRB) of Pusan National University Hospital (IRB No: 1909-016-083), a survey was conducted with doctors, nurses, and patients in the ward. All participants provided written informed consent.

1. Survey participants

The number of participants was calculated using the PASS 11 (NCSS, LLC., East Kaysville, UT, USA). The preference for MSRs was expected to be over 60%. If the width of the 95% confidence interval was within 12% and an error of 6% was allowed, the required sample size was confirmed to be 271. Considering the rate of dropouts such as abandonment and omission as 20%, a total of 325 copies were distributed. Finally, 320 copies were collected (recovery rate, 98.5%), which were used for the analysis.

2. Questionnaire

The MSR was introduced first as follows: "We are going to conduct a perception survey on MSRs for inpatients. The robot will help the staff (doctors and nurses). Autonomous driving is possible, and information delivery and education will be possible through the screen. Partial dialog (communication through speech) will be possible, and images will be collected and analyzed through depth cameras."

The questionnaire was largely composed of four items: (1) preferred external appearance, (2) perception, (3) expected utilization, (4) predicted safety accidents and their responsibilities. The preferred external appearance list is shown in Fig. 1. The questions associated with the perceptions of MSR are presented in Table 1. Questions associated with perceptions were created by mixing positive and negative questions, and the responses were answered on a Likert 5-point scale from "not at all (1 point)" to "strongly agree (5 points)." The expected utilization of MSRs is listed in Table 2. The responses were answered on a Likert 5-point scale from "not at all important (1 point)" to "very important (5 points)." In questions associated with possible safety accidents of MSRs and their responsibilities, the answer sheet of the four-or five-choice multiple types was given, and one of them was selected.

3. Statistical analysis

All statistical analyses were conducted using IBM SPSS version 22 (IBM Corp., Armonk, NY, USA) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Categorical data were analyzed using Pearson chi-square test. Continuous data were

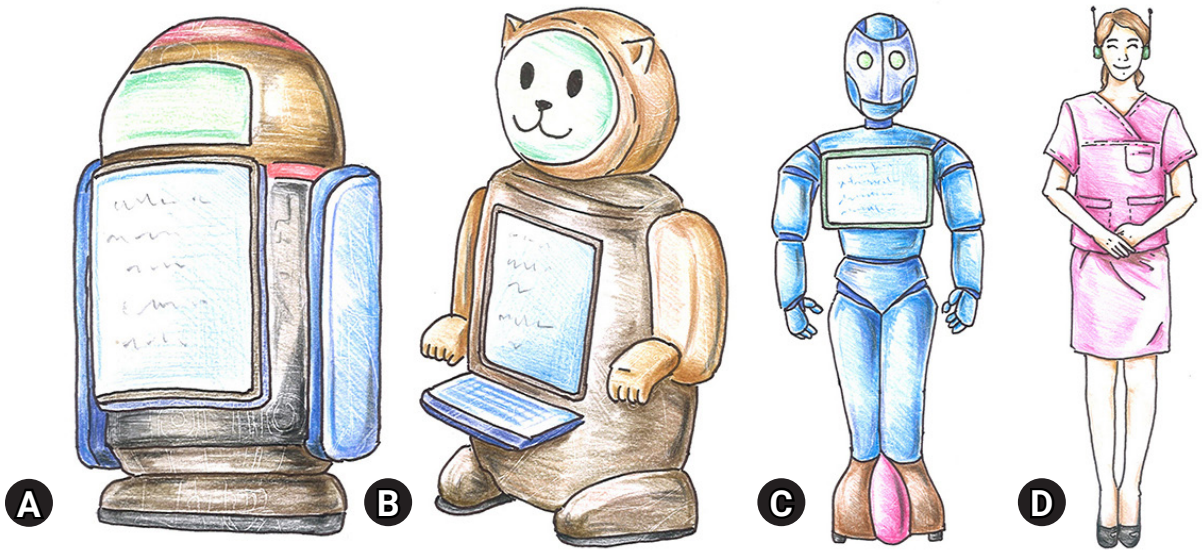

Fig. 1. List of the external appearance of medical service robots. (A) Cylindrical or square type with a screen, (B) animal type with a screen, (C) humanoid (a simplified human structure), and (D) android (very similar to human appearance).

Table 1. Questionnaire regarding perceptions of medical serviced robots in a hospital

No.	Category	Question
Q01	Positive	There will be fewer errors in measurement, transferring information, and explanation because it is a machine
Q02	Positive	There will be less stress that occurs when facing people
Q03	Positive	Better quality care and hospitalization will be possible by sharing the work of the staff
Q04	Positive	The conversation function will alleviate the anxiety that occurs during hospitalization
Q05	Negative	I don't think there are many functions that can replace people, so I don't think I will use it even in wards
Q06	Negative	There is a possibility that the robot may malfunction
Q07	Negative	It will be inconvenient to use because I am not good at handling machines
Q08	Negative	There is a possibility of a safety accident due to autonomous driving
Q09	Negative	The sensors used by the robot will be less accurate
Q10	Negative	The communication function used by robots will be less accurate
Q11	Negative	The information, such as guidance and education provided by robots, will not be of much help in actual situations
Q12	Positive	The loading of the staff will decrease when the robots share the work
Q13	Positive	When robots share medical care, patients' satisfaction during hospitalization will be improved
Q14	Positive	Overall, I agree to deploy robots in wards
Q15	Positive	Overall, the services provided by robots in wards will be reliable
Q16	Positive	Overall, the services provided by robots will help patients

Table 2. Questionnaire regarding expected utilization of medical service robots

No.	Service
S01	Checking for the ward environment (temperature, humidity, and airborne dust concentration, etc.)
S02	Analysis of gait
S03	Instructing rehabilitation methods
S04	Guiding postoperative posture and range of movement
S05	Checking for paralysis
S06	Calling the ward nurses
S07	Analysis of pain scale
S08	Analysis and improvement of depression/anxiety
S09	Analysis and improvement of stress
S10	Guiding to hospital facilities
S11	Instructing the process of admission and discharge of the hospital
S12	Informing results of imaging and laboratory findings
S13	Informing scheduled inspections
S14	Informing processes and side effects of scheduled surgeries or procedures
S15	Requesting medical certifications
S16	Checking the blood pressure and pulse
S17	Checking the temperature
S18	Checking the respiratory rate
S19	Checking the blood sugar level
S20	Checking the input and output
S21	Checking the amount of remnant intravenous fluid
S22	Guiding to the dietary plan
S23	Management of the drug administration

tested using an independent *t*-test and one-way analysis of variance with a *post hoc* Tukey test. Statistical significance was set at $p < 0.05$. Cronbach alpha coefficient was calculated to verify the reliability of the questions associated with perceptions. A scatter plot was constructed to determine the difference in preference for expected utilization between the groups.

Results

1. Characteristics of participants

A total of 320 participants responded to the survey, and their characteristics are presented in Table 3. The average age of the respondents was 39 ± 15 years.

2. Preference for the external appearance of medical service robots

We presented external images of the MSR (Fig. 1) and chose the most preferred image. B (animal type with screen, 35.0%) was selected. This was followed by A (cylindrical or square type with a screen, 27.8%) and D (android [very similar to human appearance], 22.4%). C (humanoid [a simplified human structure], 14.8%) was the least preferred. The difference in the preference for external appearance according to sex, age group, and occupation classification was not statistically identified.

Table 3. Demographic of participants

Characteristic	Patient	Doctor	Nurse	Total
Sex				
Male	53	58	6	117 (36.6)
Female	47	46	110	203 (63.4)
Age group (yr)				
Young (<41)	9	76	112	197 (61.6)
Middle (≥41, <64)	60	23	4	87 (27.2)
Elderly (≥64)	31	5	0	36 (11.2)
Total	100 (31.3)	104 (32.5)	116 (36.3)	320 (100)

Values are presented as number only or number (%).

3. Perceptions of medical service robots

Among the questions for the perception of MSRs, the positive questions were Q01–Q04 and Q12–Q16. The overall average score of these questions was 3.64 ± 0.98 of 5 points. The negative questions were Q05–Q11 and the overall average score of these questions was 3.24 ± 0.99 of 5 points. The value of Cronbach alpha for the applicability to all questions was 0.767. Cronbach alpha values for the positive and negative questions were 0.826 and 0.735, respectively. Thus, the overall reliability was acceptable. When the values of the positive and negative questions were compared, the value of the positive questions was statistically significantly higher ($p < 0.001$). The values of each question for perceptions and differences according to occupation classification are listed in Table 4.

4. Expected utilization of services provided by medical service robots

The overall average of all expected utilization was 4.05 ± 0.84 of 5 points. The value of Cronbach alpha for the applicability for all items was 0.934. The values of each item for expected utilization and differences according to occupation classification are listed in

Table 4. Statistical analysis of perceptions of medical serviced robots in a hospital

Question	Overall	Patient[a]	Doctor[b]	Nurse[c]	*p*-value	*Post hoc* analysis
Q01	3.46 ± 1.05	3.08 ± 1.12	3.70 ± 1.01	3.57 ± 0.96	<0.001	a<b,c
Q02	3.83 ± 1.00	3.49 ± 1.04	3.98 ± 0.90	3.97 ± 1.00	0.001	a<b,c
Q03	3.87 ± 0.80	3.88 ± 0.81	3.82 ± 0.81	3.92 ± 0.80	0.664	
Q04	3.22 ± 0.96	3.45 ± 0.95	3.02 ± 1.04	3.19 ± 0.86	0.009	a>b
Q12	3.58 ± 0.88	3.77 ± 0.88	3.48 ± 0.82	3.51 ± 0.91	0.400	
Q13	3.56 ± 0.78	3.71 ± 0.84	3.47 ± 0.79	3.50 ± 0.70	0.065	
Q14	3.79 ± 0.79	3.93 ± 0.68	3.65 ± 0.86	3.79 ± 0.80	0.037	a>b
Q15	3.62 ± 0.78	3.74 ± 0.80	3.56 ± 0.80	3.57 ± 0.74	0.195	
Q16	3.82 ± 0.69	3.96 ± 0.64	3.79 ± 0.70	3.73 ± 0.71	0.041	a>c
Q05	2.93 ± 0.97	2.69 ± 1.00	2.89 ± 0.99	3.18 ± 0.87	0.001	a<c
Q06	3.84 ± 0.79	3.65 ± 0.82	3.81 ± 0.80	4.04 ± 0.71	0.001	a<c
Q07	3.29 ± 0.99	3.42 ± 1.01	3.20 ± 1.02	3.26 ± 0.94	0.275	
Q08	3.62 ± 0.84	3.31 ± 1.00	3.68 ± 0.77	3.83 ± 0.65	<0.001	a<b,c
Q09	3.06 ± 0.92	2.78 ± 0.95	3.07 ± 0.92	3.30 ± 0.82	<0.001	a<c
Q10	3.36 ± 0.93	2.98 ± 1.01	3.42 ± 0.90	3.65 ± 0.78	<0.001	a<b,c
Q11	2.59 ± 0.90	2.45 ± 0.91	2.73 ± 0.91	2.58 ± 0.88	0.097	
Total (positive)	3.64 ± 0.98	3.68 ± 0.89	3.61 ± 0.90	3.64 ± 0.86	0.255	
Total (negative)	3.24 ± 0.99	3.04 ± 1.04	3.24 ± 0.97	3.41 ± 0.93	0.004	a<b<c

Values are presented as mean ± standard deviation.
Positive questions, Q01–Q04 and Q12–Q16; negative questions, Q05–Q11.

Table 5. Expected utilization of medical service robots

Service	Overall	Patient[a]	Doctor[b]	Nurse[c]	*p*-value	*Post hoc* analysis
S01	3.89 ± 0.85	4.11 ± 0.67	3.82 ± 0.97	3.77 ± 0.86	0.002	a > b,c
S02	3.87 ± 0.98	4.04 ± 0.86	3.69 ± 1.12	3.90 ± 0.91	0.044	a > b
S03	4.06 ± 0.89	4.10 ± 0.85	3.84 ± 1.00	4.22 ± 0.79	0.090	
S04	4.14 ± 0.92	4.17 ± 0.88	3.83 ± 1.02	4.39 ± 0.79	< 0.001	b < c
S05	3.98 ± 1.12	4.22 ± 0.73	3.58 ± 1.30	4.15 ± 1.12	< 0.001	a,c > b
S06	4.16 ± 0.84	4.13 ± 0.87	4.35 ± 0.84	4.02 ± 0.78	0.012	b > c
S07	3.98 ± 0.93	4.15 ± 0.81	3.79 ± 1.00	4.00 ± 0.93	0.019	a > b
S08	3.77 ± 1.11	3.97 ± 1.23	3.47 ± 0.99	3.86 ± 1.05	0.002	a > b
S09	3.71 ± 1.03	3.93 ± 1.16	3.48 ± 0.98	3.72 ± 0.93	0.011	a > b
S10	4.44 ± 0.79	4.26 ± 0.84	4.46 ± 0.76	4.57 ± 0.74	0.160	
S11	4.42 ± 0.84	4.11 ± 0.85	4.51 ± 0.86	4.61 ± 0.75	< 0.001	a < c
S12	4.27 ± 1.01	4.19 ± 0.71	4.16 ± 1.19	4.42 ± 1.04	0.111	
S13	4.34 ± 0.86	4.23 ± 0.63	4.25 ± 1.10	4.53 ± 0.74	0.005	a,b < c
S14	4.20 ± 1.05	4.21 ± 0.98	3.98 ± 1.22	4.38 ± 0.91	0.026	b < c
S15	4.28 ± 0.96	4.14 ± 0.88	4.25 ± 1.15	4.44 ± 0.83	0.35	
S16	4.15 ± 1.02	3.84 ± 1.13	4.12 ± 0.91	4.45 ± 0.93	< 0.001	a,b < c
S17	4.16 ± 1.00	3.82 ± 1.01	4.12 ± 0.95	4.48 ± 0.93	< 0.001	a,b < c
S18	4.13 ± 1.00	3.86 ± 1.14	4.04 ± 0.85	4.46 ± 0.93	< 0.001	a,b < c
S19	4.11 ± 0.96	3.80 ± 1.02	4.05 ± 0.83	4.44 ± 0.94	< 0.001	a,b < c
S20	4.16 ± 1.02	4.15 ± 1.15	3.98 ± 0.93	4.32 ± 0.96	0.031	b < c
S21	4.05 ± 0.91	4.10 ± 0.83	3.76 ± 0.99	4.28 ± 0.84	< 0.001	a,c > b
S22	4.04 ± 0.92	3.99 ± 0.85	3.82 ± 1.00	4.29 ± 0.84	0.001	a,b < c
S23	4.07 ± 0.99	4.12 ± 1.06	3.77 ± 1.01	4.29 ± 0.85	< 0.001	a,c > b
Total	4.11 ± 0.63	4.07 ± 0.58	3.96 ± 0.61	4.28 ± 0.65	< 0.001	a,b < c

Values are presented as mean ± standard deviation.

Table 5. The most expected utilization was to guide hospital facilities. In contrast, the least expected utilization was gait analysis via the MSR. The scatter plots were drawn according to classifications of occupation: patients, doctors, patients, nurses, doctors, and nurses (Fig. 2). In addition to the services presented in the questionnaire, participants' additional suggestions associated with the services provided by MSRs were as follows: transferring specimens, transferring drugs, transferring necessary supplies, managing ward supplies, emergency alerts, measurement of oxygen saturation, and notification associated with clinical work.

5. Possible safety accidents caused by medical service robots and awareness of their responsibilities

When an MSR was placed in the ward, the possible safety accidents that were selected as of greatest concern were the transmission of false information and exposure of patient information due to malfunctions (45.5%). Next, collisions due to autonomous driving (38.1%), exposure to electromagnetic waves (6.5%), and fires (6.3%) were followed. Differences in possible safety accidents according to sex, age groups, and classifications of occupation were not statistically identified. Other opinions included electric shock accidents.

In the case of such accidents, the most frequent answer to the question about the responsibility for the accident was that both the hospital and the robot manufacturing company were equally responsible (34.7%). This was followed by "the hospitals must be more responsible than the robot manufacturing company" (19.4%), "the hospitals were entirely responsible" (16.9%), "the robot manufacturing company must be more responsible than the hospital" (16.6%), and "the robot manufacturing company was entirely responsible" (12.5%). No statistical significance was observed for these responses.

The answer most frequently selected as an important factor for the safety of autonomous robots was a low-centered design (33.8%). This was followed by a soft outer material that can absorb shocks (30.7%), a height similar to that of a human (15.1%), and a slow driving speed (13.6%). Other opinions included the application of collision prevention sensors and the application of robot-only roads.

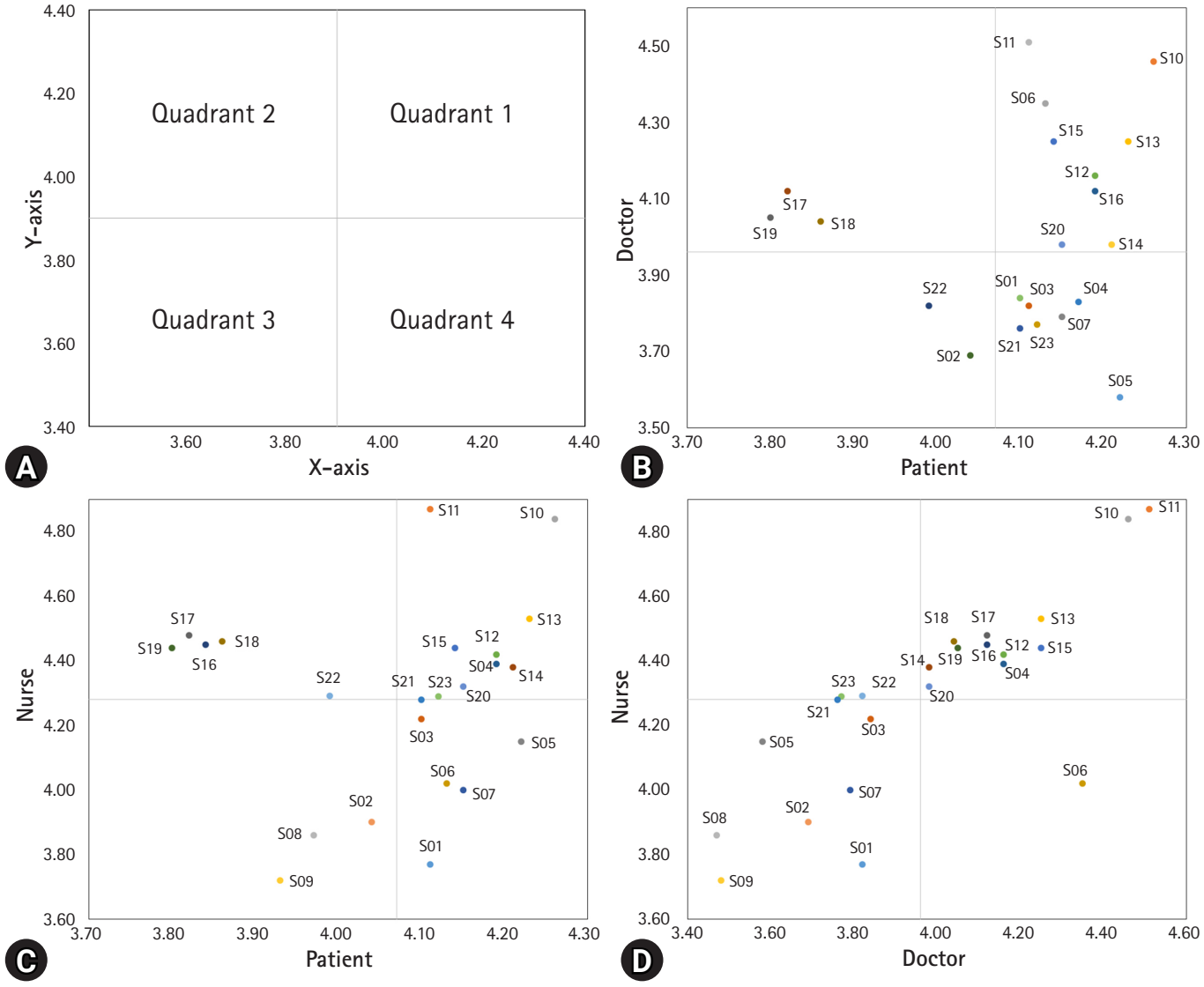

Fig. 2. Scatter plots for expected utilization. (A) Interpretation of a scatter plot. Items in quadrant 1 are preferred for both the x-axis and y-axis groups. Items in quadrant 2 are less preferred in the x-axis group but are more preferred in the y-axis group. Items in quadrant 3 are less preferred for both the x-axis and y-axis groups. Items in quadrant 4 are more preferred in the x-axis group but are less preferred in the y-axis group. (B) The scatter plot for the doctor-patient groups. (C) The scatter plot for the nurse-patient groups. (D) The scatter plot for the doctor-nurse groups.

Discussion

There have been some studies related to the external appearance of social robots to interface with a person [6-8]. Most of them have reported that an animal-like appearance is preferred over a human-like appearance in robots related to healthcare [6,7]. In this study, the preference for a non-human-like appearance was higher than that of a human-like appearance. In the case of human-like appearance, social and ethical issues can occur, so caution might be required [7]. Thus, a non-human-like appearance is appropriate. However, in the healthcare field, robots with a human-like appearance are preferred [8]. Therefore, additional studies are required to confirm this hypothesis.

Overall, the study participants had positive perceptions of MSR. In the patient group, there were statistically significant positive responses compared to medical staff (doctors and nurses), indicating that the anticipation for MSR was higher. However, even though they were negative questions, some questions exhibited high scores. In particular, scores for robot malfunctions and safety accidents were greater than the median value of the scores for negative questions, indicating concern about this. Among the positive questions, the question with the lowest score was about conversational

function, and in particular, the doctor group revealed ambivalent perception.

The overall expectation for the utilization of MSR was found to be statistically significantly higher in the nurse group and the lowest in the doctor group. Among the expected utilization of MSR, the service with the highest score was guiding to hospital facilities (S10), and the service with the lowest score was analysis and improvement of stress (S09). The doctor group expected the lowest utilization for analysis and improvement of depression or stress when hospitalized, but the patients expected relatively high efficacy. The patient group expected the highest utilization for guiding to hospital facilities. The services that were judged to show the lowest expected utilization in the patient group were various measurements such as input and output, blood pressure, temperature, respiratory rate, and blood sugar. In contrast, nurses who directly managed these measurements expected relatively high efficacy. In previous surveys related to robots, measurement and monitoring showed the highest preference for nurses, which was similar to our results [3,5]. Therefore, it can be seen that nurses prefer to apply MRS to measurement tasks. In the scatterplot analysis, the services that were in the 1st quadrant in all groups (i.e., with relatively high utilization expectations in all groups) were guiding to hospital facilities (S10), instructing the process of admission and discharge of the hospital (S11), informing results of imaging and laboratory findings (S12), informing scheduled inspections (S13), informing processes and side effects of scheduled surgeries or procedures (S14), requesting medical certifications (S15), and checking the input and output (S20). It was mainly related to information delivery to patients or guardians and administrative work processing. In contrast, the service in the third quadrant in all groups, that is, with relatively low utilization expectation in all groups, was S02. There have been many studies related to gait analysis using artificial intelligence [9]. However, it was revealed that expectations were relatively low when applying this function through MSRs.

To use the MSR in hospital wards, it must be able to move to the bed. This was because it was the patient who faced MSR primarily, and the patient was often unable to move out of bed during the acute phase. Thus, our consortium was trying to apply autonomous driving and was concerned about the physical accidents caused by it. However, the most worrisome accident in the survey was exposure to personal information. Therefore, it is necessary to take measures to prevent such accidents when operating an MSR. While the issue of legal responsibility for the occurrence of safety accidents caused by various robots has been actively discussed recently, there has been little discussion about the legal issue of accidents involving robots related to healthcare [10]. Participants in this study thought that the overall responsibility of the robot user (hospital) was greater than that of the robot manufacturer in the case of safety accidents. However, since the judgment of the relevant expert was important in legal matters, more research is needed in this area.

In this study, we investigated the perception associated with MSRs used in hospital wards. The recognition of MSRs used in hospital wards was generally positive, and the overall expected utilization was high. In particular, MSRs were expected to be highly effective in delivering various types of information and measuring the input and output. Furthermore, it is also necessary to recognize safety accidents for such robots, and sufficient attention is required when developing and manufacturing robots.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

This work was supported by the Technology Innovation Program of the Ministry of Trade, Industry & Energy (MOTIE), funded by the South Korea government (grant number 20000515).

Author contributions

Conceptualization: JHL, MK, DHK, IHH; Data curation: JHL, JH, JYP, MK, DHK, JIL, KHN; Formal analysis: JML, JIL, IHH; Funding acquisition: MK, DHK, IHH; Methodology: JHL, KHN; Project administration, Resources, Supervision: IHH; Investigation, Software: JHL; Visualization: JML; Validation: MK, DHK; Writing - original draft: JHL, JH, JYP, MK; Writing - review & editing: JML, DHK, JIL, KHN, IHH.

ORCID

Jung Hwan Lee, https://orcid.org/0000-0002-1393-7105
Jae Meen Lee, https://orcid.org/0000-0002-5708-1644
Jaehyun Hwang, https://orcid.org/0000-0002-6730-2092
Joo Young Park, https://orcid.org/0000-0001-5646-0899
Mijeong Kim, https://orcid.org/0000-0003-3307-0315
Dong Hwan Kim, https://orcid.org/0000-0001-8982-7917
Jae Il Lee, https://orcid.org/0000-0003-1412-4146
Kyoung Hyup Nam, https://orcid.org/0000-0002-3749-4660
In Ho Han, https://orcid.org/0000-0001-7193-6533

References

1. Nam KH, Kim DH, Choi BK, Han IH. Internet of things, digi-

tal biomarker, and artificial intelligence in spine: current and future perspectives. Neurospine 2019;16:705–11.
2. Wang TM, Tao Y, Liu H. Current researches and future development trend of intelligent robot: a review. Int J Autom Compt 2018;15:525–46.
3. Lee JY, Song YA, Jung JY, Kim HJ, Kim BR, Do HK, et al. Nurses' needs for care robots in integrated nursing care services. J Adv Nurs 2018;74:2094–105.
4. Koh DH, Jang WS, Park JW, Ham WS, Han WK, Rha KH, et al. Efficacy and safety of robotic procedures performed using the da Vinci robotic surgical system at a single institute in Korea: experience with 10000 cases. Yonsei Med J 2018;59:975–81.
5. Hong E, Shin S. Nurses' perceptions of care robots in long-term care facilities. J Korean Gerontol Nurs 2019;21:22–32.
6. Lohse M, Hegel F, Swadzba A, Rohlfing K, Wachsmuth S, Wrede B. What can I do for you? Appearance and application of robots. Paper presented at: The 33rd Annual Convention of the Society for the Study of Artificial Intelligence and the Simulation of Behaviour; 2007 Apr 2–5; Tyne, UK. New York: Curran Associates, Inc.; 2007. p. 121–6
7. Wu YH, Fassert C, Rigaud AS. Designing robots for the elderly: appearance issue and beyond. Arch Gerontol Geriatr 2012; 54:121–6.
8. Hegel F, Lohse M, Wrede B. Effects of visual appearance on the attribution of applications in social robotics. Paper presented at: The 18th IEEE International Symposium on Robot and Human Interactive Communication; 2009 Sep 27–Oct 2; Toyama, Japan. Piscataway (NJ): IEEE; 2009. p. 64–71.
9. Prakash C, Kumar R, Mittal N. Recent developments in human gait research: parameters, approaches, applications, machine learning techniques, datasets and challenges. Artif Intell Rev 2018;49:1–40.
10. Kirkpatrick K. Legal issues with robots. Commun ACM 2013; 56:17–9.

Original article

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):124-132
https://doi.org/10.12701/yujm.2021.01347

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

The clinical outcomes of second-line chemotherapy in patients with advanced pancreatic cancer: a retrospective study

Hyun yeb Jung, Eun Mi Lee

Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan Korea

Background: Despite recent advances in first-line chemotherapy for advanced pancreatic cancer, standard treatment after the failure of initial chemotherapy has not been established. Hence, we aimed to retrospectively analyze the clinical characteristics and outcomes of second-line chemotherapy in patients with advanced pancreatic cancer.

Methods: We reviewed the clinical data of patients with advanced pancreatic cancer who underwent palliative chemotherapy at Kosin University Gospel Hospital between January 2013 and October 2020.

Results: Among 366 patients with advanced pancreatic cancer who had received palliative chemotherapy, 104 (28.4%) underwent at least one cycle of second-line chemotherapy. The median age of the patients at the time of initiating second-line treatment was 62 years (interquartile range, 57–62 years), and 58.7% (61 patients) of them were male. The common second-line chemotherapy regimens were 5-fluorouracil (FU) plus leucovorin, irinotecan, and oxaliplatin (33 patients, 31.7%); gemcitabine/nab-paclitaxel (29, 27.9%), gemcitabine±erlotinib (13, 12.5%); and oxaliplatin and 5-FU/leucovorin (12, 11.5%). The median overall survival (OS) and progression-free survival were 6.4 months (95% confidence interval [CI], 4.5–8.6 months) and 4.5 months (95% CI, 2.7–6.3 months), respectively. In a multivariate analysis, poor performance status (PS) (hazard ratio [HR], 2.247; $p=0.021$), metastatic disease (HR, 2.745; $p=0.011$), and elevated carcinoembryonic antigen (CEA) levels (HR, 1.939; $p=0.030$) at the beginning of second-line chemotherapy were associated with poor OS.

Conclusion: The survival outcome of second-line chemotherapy for advanced pancreatic cancer remains poor. However, PS, disease extent (locally advanced or metastatic), and CEA level may help determine patients who could benefit from second-line treatment.

Keywords: Chemotherapy; Pancreatic cancer; Performance status; Prognostic factor

Introduction

Although recent advances in solid tumor treatment have dramatically improved patients' survival, the prognosis of pancreatic cancer remains dismal, with a 5-year survival rate of 9% in all stages [1]. Considering that surgical resection is possible only in 15%–20% of patients at diagnosis and most patients relapse after surgery, palliative chemotherapy is the mainstay of treatment for irresectable or recurrent diseases. Over the last decade, in two randomized phase 3 trials (the PRODIGE and MPACT trials), intensive combination chemotherapies, such as 5-fluorouracil (FU) plus leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine/nab-paclitaxel, have shown a more improvement in overall survival (OS) as the initial palliative chemotherapy than gemcit-

Received: July 22, 2021 • **Revised:** September 7, 2021 • **Accepted:** September 14, 2021
Corresponding author: Eun Mi Lee, MD
Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea
Tel: +82-51-990-5820 • Fax: +82-51-990-5820 • E-mail: byule00@hanmail.net

abine monotherapy, which was the standard treatment until then [2,3]. In a phase 3 trial (NCIC CTG PA.3 trial]), the addition of erlotinib to gemcitabine demonstrated statistically significant improvement in OS compared with gemcitabine monotherapy. However, small survival gain (median OS, 6.2 months vs. 5.9 months; hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69–0.99; $p = 0.038$), increased toxicity risk, and high cost have limited the efficacy of the addition of erlotinib to gemcitabine [4]. Thus, FOLFRINOX and gemcitabine/nab-paclitaxel are the most widely used front-line chemotherapy regimens in patients with excellent performance status (PS), and gemcitabine monotherapy remains an option for the treatment of patients with poor OS. However, no subsequent treatment after failure of the initial chemotherapy has been established.

Three randomized phase 3 clinical trials have been conducted for second-line chemotherapy for advanced pancreatic cancer. The CONKO-003 trial showed that the combination of oxaliplatin and 5-FU/leucovorin (FOLFOX) was better in extending OS as second-line chemotherapy than 5-FU/leucovorin in patients with gemcitabine-refractory advanced pancreatic cancer (5.9 months vs. 2.3 months; HR, 0.66; 95% CI, 0.48–0.91; $p = 0.010$) [5]. Conversely, the PANCREOX trial showed that FOLFOX did not improve OS, compared with infusional 5-FU/leucovorin (6.1 months vs. 9.9 months; HR, 1.78; 95% CI, 1.08–2.93; $p = 0.024$) after gemcitabine failure [6]. This difference seems to be explained by the PS imbalance between the study groups and a possible crossover after disease progression in the PANCREOX trial. Recently, the NAPOLI-1 trial assessed the effects of nanoliposomal irinotecan, a new irinotecan formulation, alone or in combination with 5-FU/leucovorin, in patients with advanced pancreatic cancer after the failure of gemcitabine-based chemotherapy. In this trial, the group receiving nanoliposomal irinotecan combined with 5-FU/leucovorin had a longer OS than the group receiving 5-FU/leucovorin (6.1 months vs. 4.2 months; 95% CI, 0.49–0.92; $p = 0.012$); hence, the combination of nanoliposomal irinotecan and 5-FU/leucovorin was approved as subsequent chemotherapy after failure of gemcitabine-based chemotherapy [7].

However, these studies on second-line chemotherapy were conducted in patients who previously underwent gemcitabine, and no randomized trials focusing on treatment after the failure of a more intensive chemotherapy, such as FOLFIRINOX or gemcitabine/nab-paclitaxel have been conducted. Moreover, given that patients with advanced pancreatic cancer have different clinical characteristics and situations in a real clinical setting, their second-line treatment should be individualized. In this retrospective study, we aimed to report the clinical characteristics and results of second-line chemotherapy for patients with advanced pancreatic cancer who failed initial chemotherapy in actual clinical practice.

Methods

Ethical statements: We obtained the patients' clinical features, treatment information, and outcomes from the medical records. The Institutional Review Board (IRB) of Kosin University Gospel Hospital approved this study (IRB No: KUGH 2021-07-018). The requirement for informed consent was waived because of the retrospective nature of the study.

1. Patients

This retrospective study reviewed the clinical data of patients with advanced pancreatic cancer who had received palliative chemotherapy at Kosin University Gospel Hospital (Busan, Korea) between January 2013 and October 2020.

We included patients who had pathologically confirmed pancreatic adenocarcinoma with locally advanced or metastatic disease and underwent at least one cycle of second-line chemotherapy. If chemotherapy was performed after the disease had progressed within 6 months of the completion of adjuvant chemotherapy, it was considered second-line chemotherapy. Histological findings other than adenocarcinoma were excluded.

2. Statistical analysis

Progression-free survival (PFS) was calculated from the date of starting second-line chemotherapy to the date of disease progression, and OS was calculated from the date of starting second-line chemotherapy to the date of death. The duration of clinical benefit was defined as the time interval from the time of response, including complete response (CR), partial response (PR), and stable disease (SD), to the date of disease progression. The median PFS and OS were estimated using the Kaplan-Meier method. The Cox proportional hazard model was used for univariate and multivariate analyses of prognostic factors associated with PFS and OS. Statistical analysis was performed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA), and statistical significance was set at $p < 0.05$.

Results

1. Patient characteristics

This study included 366 patients diagnosed with advanced pancreatic cancer who had received palliative chemotherapy between the abovementioned periods. Among them, 104 (28.4%) underwent

at least one cycle of second-line chemotherapy. Table 1 summarizes the patient characteristics. The median age of the patients at the beginning of second-line treatment was 62 years (interquartile range [IQR], 57–62 years), and 89% of the patients had an excellent Eastern Cooperative Oncology Group (ECOG) PS (0 or 1). At the time of initiating the second-line chemotherapy, 82 patients (78.8%) had metastatic disease. As first-line chemotherapy, 38 (36.5%), 26 (25.0%), and 34 patients (32.7%) received gemcitabine (with or without erlotinib), gemcitabine/nab-paclitaxel, and FOLFIRINOX, respectively. Tumor response to first-line chemotherapy was assessable in 82 patients, and response rate according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 was 20.7 % (none of the patients had a CR and 17 patients achieved a PR).

Table 1. Baseline characteristic of patients who received second-line chemotherapy

Characteristic	Data
No. of patients	104
Age (yr)[a]	62 (57–62)
Sex, male:female	61 (58.7):43 (41.3)
Smoking	
Never	74 (71.2)
Current or former smoking	30 (28.8)
Diabetes mellitus	42 (40.4)
EGOG PS[a]	
0–1	89 (85.6)
≥2	15 (14.4)
Primary tumor location	
Head	43 (41.3)
Body	27 (26.0)
Tail	34 (32.7)
Disease extent[a]	
Locally advanced	22 (21.2)
Metastatic	82 (78.8)
Metastasis[a]	
Liver	53 (51.0)
Peritoneal	30 (28.8)
Lung	25 (24.0)
Bone	9 (8.7)
Anemia[a]	87 (83.7)
Hypoalbuminemia[a]	18 (17.3)
CA19-9[a] (U/mL)	221 (41–2,166)
CEA[a] (ng/mL)	6.95 (3.63–25.2)
Regimen of first-line chemotherapy	
Gemcitabine ± erlotinib	38 (36.5)
Gemcitabine+nab-paclitaxel	26 (25.0)
FOLFIRINOX	34 (32.7)
Others[b]	6 (5.8)
Response rate of first-line chemotherapy (n = 82)	17 (20.7)
Duration of first-line chemotherapy (mo)	4.5 (2.4–7.1)

Values are presented as number only, median (interquartile range), or number (%).
ECOG PS, Eastern Cooperative Oncology Group performance status; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; FOLFIRINOX, 5-fluorouracil/leucovorin, irinotecan, and oxaliplatin.
[a]At start of second-line chemotherapy. [b]Gemcitabine+cisplatin, 5-fluorouracil (FU), 5-FU+leucovorin, 5-FU+cisplatin (one patient each), gemcitabine+capecitabine (two patients).

2. Treatment of second-line chemotherapy

Tables 2 and 3 list the treatment patterns and regimens used for second-line chemotherapy according to first-line regimens. For second-line chemotherapy, FOLFIRINOX, gemcitabine/nab-paclitaxel, gemcitabine ± erlotinib, and FOLFOX were administered to 33 (31.7%), 29 (27.9%), 13 (12.5%), and 12 patients (11.5%), respectively. Of the 38 patients who received gemcitabine ± erlotinib as a first-line regimen, 12 (31.6%), 8 (21.1%), and 7 (18.4%) received FOLFIRINOX, FOLFOX, and gemcitabine/nab-paclitaxel as their subsequent chemotherapy regimens, respectively. Of the 26 patients whose gemcitabine/nab-paclitaxel therapy failed,

Table 2. Treatment of second-line chemotherapy (n=104)

Treatment	Data
Chemotherapy regimen	
FOLFIRINOX	33 (31.7)
Gemcitabine+nab-paclitaxel	29 (27.9)
Gemcitabine ± erlotinib	13 (12.5)
FOLFOX	12 (11.5)
5-FU+cisplatin	7 (6.7)
5-FU+doxorubicin+mitomycin	3 (2.9)
Gemcitabine+cisplatin	2 (1.9)
Others[a]	5 (4.8)
Cycle of chemotherapy	3 (2–6)
Tumor response (n = 86)	
Partial response	2 (2.3)
Stable disease	33 (38.4)
Progressive disease	31 (36.0)
Not evaluable	20 (23.3)
Duration of clinical benefit (mo) (n = 35)	4.5 (2.1–7.0)
Reason for treatment discontinuation	
Disease progression	52 (50.0)
Toxicity/PS deterioration	47 (45.2)
Others	5 (4.8)
Duration of second-line chemotherapy (mo)	1.9 (0.6–4.6)

Values are presented as number (%) or median (interquartile range).
FOLFIRINOX, 5-fluorouracil (FU)/leucovorin, irinotecan, and oxaliplatin; FOLFOX, 5-FU/leucovorin+oxaliplatin; PS, performance status.
[a]5-FU+doxorubicin, 5-FU+liposomal irinotecan+leucovorin, 5-FU, S-1, and atezolizumab (one patient each).

Table 3. The second-line chemotherapy regimens in patients with advanced pancreatic cancer according to the first-line regimens

The second-line regimen	First-line regimen			
	Gemcitabine (±erlotinib)	Gemcitabine+nab-paclitaxel	FOLFIRINOX	Others
Gemcitabine (±erlotinib)	0 (0)	1 (3.8)	12 (35.3)	0 (0)
Gemcitabine+nab-paclitaxel	7 (18.4)	0 (0)	21 (61.8)	0 (0)
FOLFIRINOX	12 (31.6)	17 (65.4)	0 (0)	4 (66.7)
FOLFOX	8 (21.1)	3 (11.5)	0 (0)	1 (16.7)
5-FU+cisplatin	6 (15.8)	1 (3.8)	0 (0)	0 (0)
Others	5 (13.2)[a]	4 (15.4)[b]	1 (2.9)	1 (16.7)
Total	38 (100)	26 (100)	34 (100)	6 (100)

Values are presented as number (%).
FOLFIRINOX, 5-fluorouracil (FU)+leucovorin, irinotecan, and oxaliplatin; FOLFOX, 5-FU/leucovorin+oxaliplatin.
[a]5-FU+doxorubicin+mitomycin (3 patients), 5-FU+doxorubicin, gemcitabine+cisplatin (one patient each). [b]Nanoliposomal irinotecan+5-FU+leucovorin, 5-FU+leucovorin, gemcitabine+cisplatin, S-1 (one patient each).

20 (76.9%) received oxaliplatin-based chemotherapy as a second-line regimen (FOLFOX and FOLFIRINOX in 3 and 17 patients, respectively). The majority of the 34 patients (97.1%) who underwent first-line FOLFIRINOX received gemcitabine-based chemotherapy (gemcitabine ± erlotinib and gemcitabine/nab-paclitaxel in 12 and 21 patients, respectively).

A median of three cycles of second-line chemotherapy (IQR, 2–6 cycles) was administered. Eighty-six of the 104 patients had a measurable disease based on the RECIST version 1.1, and tumor responses were assessed in these patients. None of the patients achieved a CR. Two patients had PR, and 33 patients had SD. The clinical benefit rate, including CR, PR, and SD, was 40.7% (35 patients), and the median duration of clinical benefit was 4.5 months (IQR, 2.1–7.0 months). Among the 17 patients who had a PR in first-line chemotherapy, none achieved a PR, but 9 patients (52.9%) attained an SD. Second-line chemotherapy was discontinued in 21 (20.2%) patients before the first planned follow-up point due to disease progression or PS deterioration. At the first response evaluation, disease progression was observed in 31 patients (29.8%). Furthermore, 47 patients (45.2%) discontinued treatment because of chemotherapy toxicity or PS deterioration. Two patients died of septic shock due to chemotherapy-induced neutropenia; one had been administered gemcitabine/nab-paclitaxel and the other had been administered FOLFIRINOX.

3. Survivals and prognostic factors

For a median follow-up of 16.8 months, the median PFS was 4.5 months (95% CI, 2.7–6.3 months) (Fig. 1A). Additionally, the median OS was 6.4 months (95% CI, 4.5–8.6 months), and the 1-year survival rate was 25.3% (Fig. 1B).

Tables 4 and 5 present the univariate and multivariate analyses of potential prognostic factors associated with survival in patients with advanced pancreatic cancer who underwent second-line che-

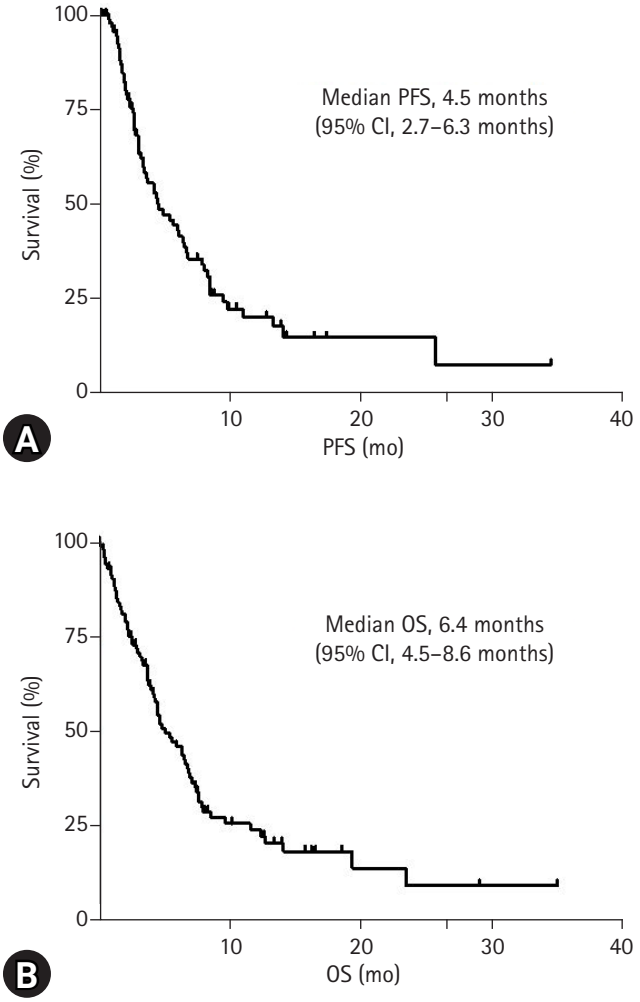

Fig. 1. Kaplan-Meier survival after second-line chemotherapy initiation. (A) Progression-free survival (PFS) after second-line chemotherapy initiation in patients with advanced pancreatic cancer. (B) Overall survival (OS) after second-line chemotherapy initiation in patients with advanced pancreatic cancer. CI, confidence interval.

Table 4. Univariate and multivariate analysis on PFS for second-line chemotherapy

Variable	Median PFS (mo)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
EGOG PS[a]					
0–1	4.5	1.070 (0.426–2.684)	0.886		
≥2	6.0				
Diabetes mellitus					
No	3.4	0.577 (0.345–0.965)	0.033	0.608 (0.355–1.043)	0.071
Yes	6.8				
Disease extent[a]					
Locally advanced	9.8	3.082 (1.588–5.984)	0.001	2.728 (1.205–6.178)	0.016*
Metastatic	3.6				
Liver metastasis[a]					
No	6.1	1.811 (1.103–2.976)	0.017	1.080 (0.580–2.011)	0.808
Yes	3.2				
Lung metastasis[a]					
No	4.9	1.797 (1.005–3.215)	0.045	1.158 (0.606–2.211)	0.657
Yes	3.4				
Bone metastasis[a]					
No	5.4	5.512 (2.094–12.677)	<0.001	3.143 (1.150–8.592)	0.026*
Yes	1.8				
CA19-9 (U/mL)					
<221	5.7	1.016 (0.618–1.670)	0.951		
≥221	3.7				
CEA[a] (ng/mL)					
Normal (≤5.5)	5.7	1.197 (0.705–2.033)	0.507		
Elevation (>5.5)	4.2				

PFS, progression-free survival; HR, hazard ratio; CI, confident interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.
[a]At start of second-line chemotherapy.
*$p<0.05$.

motherapy. Univariate analysis revealed that the absence of diabetes mellitus, the presence of metastatic disease, liver metastasis, and bone metastases at the time of initiating second-line treatment were associated with lower PFS. In the multivariate analysis, metastatic disease (HR, 2.728; 95% CI, 1.205–6.178; $p=0.016$) and bone metastasis (HR, 3.143; 95% CI, 1.150–8.592; $p=0.026$) at the time of initiating second-line were statistically significant (Table 4). In the univariate analysis of OS, poor ECOS PS (≥2), metastatic disease, liver metastasis, bone metastasis, and elevated serum carcinoembryonic antigen (CEA) levels at the time of initiating the second-line treatment were associated with lower OS. Among these factors, poor ECOG PS (≥2) (HR, 2.247; 95% CI, 1.129–4.474; $p=0.021$), metastatic disease (HR, 2.745; 95% CI, 1.260–5.983; $p=0.011$), and elevated serum CEA level (HR, 1.939; 95% CI, 1.065–3.530; $p=0.030$) at the time of initiating the second-line treatment were statistically significant in the multivariate analysis (Table 5).

Discussion

Recently, intensive initial chemotherapy using FOLFIRINOX or gemcitabine/nab-paclitaxel has improved the survival of patients with advanced pancreatic cancer [2,3]. However, the prognosis of advanced pancreatic cancer remains poor, with no standard treatment after the failure of initial chemotherapy. Hence, the present study retrospectively analyzed the clinical characteristics and outcomes of subsequent chemotherapy in patients with advanced pancreatic cancer after the failure of initial chemotherapy in clinical practice. The median OS after the start of second-line chemotherapy was 6.4 months (95% CI, 4.5–8.6 months), similar to the recent retrospective reports of second-line chemotherapy for advanced pancreatic cancer in the real-world setting (5.2–8.1 months) [8-10]. Excellent PS, locally advanced disease, and normal CEA level at the time of second-line treatment initiation were associated with better OS.

Table 5. Univariate and multivariate analysis on OS for second-line chemotherapy

Variable	Median OS (mo)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
EGOG PS[a]					
0-1	7.2	2.367 (1.330–5.217)	0.004	2.247 (1.129–4.474)	0.021*
≥2	2.3				
Diabetes mellitus					
No	5.9	0.784 (0.488–1.258)	0.311		
Yes	8.3				
Disease extent[a]					
Locally advanced	29.4	3.380 (1.719–6.644)	<0.001	2.745 (1.260–5.983)	0.011*
Metastatic	5.5				
Liver metastasis[a]					
No	8.0	2.780 (1.678–4.607)	<0.001	1.324 (0.714–2.456)	0.373
Yes	5.5				
Lung metastasis[a]					
No	8.0	1.340 (0.793–2.264)	0.272		
Yes	4.8				
Bone metastasis[a]					
No	8.0	2.596 (1.215–5.547)	0.011	2.136 (0.964–4.737)	0.062
Yes	4.9				
CA19-9 (U/mL)					
<221	8.0	1.396 (0.875–2.226)	0.16		
≥221	5.7				
CEA[a] (ng/mL)					
Normal (≤5.5)	9.3	2.006 (1.177–6.419)	0.009	1.939 (1.065–3.530)	0.030*
Elevation (>5.5)	5.4				

OS, overall survival; HR, hazard ratio; CI, confident interval; ECOG PS, Eastern Cooperative Oncology Group performance status; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.
[a]At start of second-line chemotherapy.
*$p<0.05$.

Advanced pancreatic cancer progresses quickly, and once it begins to progress after the initial treatment, the patient's PS deteriorates rapidly; hence, the decision to perform subsequent treatment is challenging. Nagrial et al. [11] systematically reviewed 24 prospective clinical trials of subsequent chemotherapy in patients with advanced pancreatic cancer who previously received gemcitabine-based chemotherapy between 1988 and 2012. They reported that 43% of the patients underwent subsequent chemotherapy and that the utilization rate significantly increased from studies published pre-2007 to those published post-2007 (35%–48%; $p=0.0015$). The MPACT and PRODIGE trials reported that the rates of utilizing second-line chemotherapy were 38% and 47%, respectively [2,3]. In our study, it was 28.4%, which was slightly lower than in these prospective studies, possibly because the prospective clinical trials generally included patients with a better PS than in actual clinical practice.

After the failure of initial chemotherapy in patients with advanced pancreatic cancer, those who only received supportive care showed dismal survival (approximately 2 months) compared with those who underwent second-line treatment [12]. The CONKO phase 3 trial demonstrated that OS was longer when administering FOLFOX as a second-line treatment than providing the best supportive care in patients with advanced pancreatic cancer (4.8 months vs. 2.3 months; 95% CI, 0.24–0.83 months; $p=0.008$); however, this trial was stopped prematurely because of insufficient recruitment (best supportive care was not accepted by patients and physicians) [13]. Although the clinical benefit of second-line chemotherapy is marginal, survival can be improved by providing appropriate subsequent treatment in selected patients. Therefore, patients who will benefit from subsequent chemotherapy after failure of the initial treatment must be identified.

Several studies have reported factors that can predict the survival outcomes of patients who undergo second-line chemotherapy [9,10,14-18]. Among several clinical and biochemical variables, PS

is one of the most common and important prognostic factors in patients receiving second-line chemotherapy [9,14-17]. Consistent with these studies, patients with an excellent ECOG PS score (0 or 1) in our study had longer survival than those with poor PS. Patients with an excellent PS could be offered aggressive treatment to prolong their survival and manage their symptoms. Therefore, PS should be regarded as an important prognostic factor in patients receiving not only second-line but also first-line chemotherapy. A meta-analysis of 12 phase 3 randomized studies for the first-line chemotherapy of metastatic pancreatic cancer demonstrated that patients with a poor ECOG PS had a worse prognosis than those with an excellent ECOG PS (HR for OS, 1.45; 95% CI, 1.21–1.74; $p < 0.001$) [19]. PS was also considered in selecting the initial chemotherapy regimen. Intensive chemotherapy regimens, such as FOLFIRINOX or gemcitabine/nab-paclitaxel, are recommended for patients with an excellent ECOG PS (0 or 1), whereas gemcitabine monotherapy is an option for the treatment of patients with an ECOG PS 2 [20,21].

Apart from excellent PS, locally advanced disease and normal CEA level at the time of initiating the second-line chemotherapy were associated with prolonged OS in our study. Our study revealed that locally advanced disease was associated with better survival, which is consistent with other retrospective studies [9,17]. In several studies, serum CA 19-9 levels at the beginning of second-line chemotherapy were reported as a prognostic factor, but in our study, this factor showed no significance [10,15,17]. Meanwhile, CEA level was associated with OS in our study, but other studies showed no such association; thus, it remains unclear whether CEA level is a significant prognostic factor. Considering the heterogeneity of patients who underwent second-line treatment, the prognostic factors of survival outcomes have been reported differently and, have not been established. Vienot et al. [16] analyzed a large cohort of 395 patients with advanced pancreatic cancer and developed a prognostic nomogram to predict patient survival for second-line chemotherapy. They identified nine independent prognostic factors: age, smoking status, liver metastasis, PS, pain, jaundice, ascites, duration of first-line chemotherapy, and second-line chemotherapy type. Given the lack of unified prognostic factors to predict patient survival for second-line chemotherapy, further prospective clinical studies are needed to validate these variables.

Randomized trials on subsequent chemotherapy for patients with advanced pancreatic cancer who failed in the initial chemotherapy are limited, and no acceptable standard regimen for subsequent chemotherapy has been established. The only second-line chemotherapy regimen that showed a survival benefit in a phase 3 trial is the combination of nanoliposomal irinotecan and 5-FU/leucovorin (the NAPOLRI trial) [7]. However, the NAPOLRI trial did not include patients who underwent first-line FOLFIRINOX, and the value of using such combined regimen after FOLFIRINOX remains vague. In our study, only one patient received a second-line regimen containing nanoliposomal irinotecan, probably because nanoliposomal irinotecan is not covered by public insurance in Korea.

The optimal sequence of palliative chemotherapy for advanced pancreatic cancer remains unclear. Generally, first-line chemotherapy regimens and PS are considered when selecting second-line regimens. For patients who were administered prior gemcitabine-based regimens, 5-FU-based regimens are acceptable subsequent treatment options. Gemcitabine-based regimens can be administered to patients previously treated with 5-FU-based chemotherapy. Intensive chemotherapy regimens, such as FOLFIRINOX and gemcitabine/nab-paclitaxel, can be considered after failure of gemcitabine-based regimens and FOLFIRINOX, respectively, but no randomized trials have been conducted. In a single-arm phase 2 trial, administering FOLFIRINOX after gemcitabine failure showed a promising outcome, with a median OS of 8.5 months (95% CI, 5.6–11.4 months), but 41.0% of the patients developed grade 3 or 4 neutropenia despite using an attenuated regimen [22].

Administering gemcitabine/nab-paclitaxel after first-line FOLFIRINOX failure showed a better median OS of 8.8 months (95% CI, 6.2–9.7 months) in the AGEO trial than gemcitabine monotherapy (3.6–5.7 months) in several retrospective trials [23-26]. However, grade 3 or 4 adverse events occurred in 40% of the patients [23]. Second-line FOLFIRINOX and gemcitabine/nab-paclitaxel have shown promising OS, but with high toxicities; thus, they should be administered to patients with an excellent PS and a favorable comorbidity profile. In our study, FOLFIRINOX was administered to 45.3% of the patients who previously underwent gemcitabine-based chemotherapy (29 of 64 patients), and gemcitabine/nab-paclitaxel was administered to 61.8% of the patients who failed FOLFIRINOX (21 of 34 patients).

This study has several limitations. First, it has a retrospective design; thus, all data were only acquired by reviewing the medical records. Therefore, the results of prognostic factors to predict survival outcomes should be interpreted with caution. Second, the patients received various chemotherapy regimens; hence, defining the benefit of a certain regimen for second-line chemotherapy is inappropriate. Further clinical studies are needed to determine the appropriate sequences for chemotherapy. In addition, the characteristics of the patients included in this retrospective analysis were heterogeneous, and the duration of second-line chemotherapy was short (median, 1.9 months). Because of these limitations, our analysis is insufficient to verify the actual effects of second-line chemo-

therapy for advanced pancreatic cancer, and caution is needed to interpret these outcomes.

In conclusion, our findings revealed that the clinical outcome of second-line chemotherapy for advanced pancreatic cancer is still poor, with a median OS of 6.4 months (95% CI, 4.5–8.6 months), which is consistent with other retrospective studies. Nonetheless, some factors such as PS, disease extent (locally advanced or metastatic), and CEA level at the beginning of second-line treatment could help identify patients who may benefit from second-line chemotherapy. However, because this was a small retrospective study including patients with heterogeneous characteristics, the results of this analysis should be cautiously interpreted, and further prospective clinical trials are needed to evaluate the effect of second-line chemotherapy on advanced pancreatic cancer.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization, Data curation, EML; Writing-original draft: EML, HyJ; Writing-review & editing: EML, HyJ.

ORCID

Hyun yeb Jung, https://orcid.org/0000-0001-7900-6277
Eun Mi Lee, https://orcid.org/0000-0002-0746-8883

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30.
2. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
3. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.
4. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960–6.
5. Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol 2014;32:2423–9.
6. Gill S, Ko YJ, Cripps C, Beaudoin A, Dhesy-Thind S, Zulfiqar M, et al. PANCREOX: a randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. J Clin Oncol 2016;34:3914–20.
7. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387:545–57.
8. Ramaswamy A, Parthiban S, Malhotra M, Kothari R, Goel A, Bhargava P, et al. Outcomes with second-line chemotherapy in advanced pancreatic cancers: a retrospective study from a tertiary cancer center in India. Indian J Cancer 2018;55:144–7.
9. Tsang ES, Wong HL, Wang Y, Renouf DJ, Cheung WY, Lim HJ, et al. Outcomes and characteristics of patients receiving second-line therapy for advanced pancreatic cancer. Am J Clin Oncol 2019;42:196–201.
10. Gränsmark E, Bågenholm Bylin N, Blomstrand H, Fredrikson M, Åvall-Lundqvist E, Elander NO. Real world evidence on second-line palliative chemotherapy in advanced pancreatic cancer. Front Oncol 2020;10:1176.
11. Nagrial AM, Chin VT, Sjoquist KM, Pajic M, Horvath LG, Biankin AV, et al. Second-line treatment in inoperable pancreatic adenocarcinoma: a systematic review and synthesis of all clinical trials. Crit Rev Oncol Hematol 2015;96:483–97.
12. Rahma OE, Duffy A, Liewehr DJ, Steinberg SM, Greten TF. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. Ann Oncol 2013;24:1972–9.
13. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer 2011;47:1676–81.
14. Kim ST, Choi YJ, Park KH, Oh SC, Seo JH, Shin SW, et al. A prognostic model to identify patients with advanced pancreas adenocarcinoma who could benefit from second-line chemotherapy. Clin Oncol (R Coll Radiol) 2012;24:105–11.
15. Sinn M, Dälken L, Striefler JK, Bischoff S, Schweitzer N, Pelzer U, et al. Second-Line treatment in pancreatic cancer patients:

who profits? Results from the CONKO Study Group. Pancreas 2016;45:601–5.
16. Vienot A, Beinse G, Louvet C, de Mestier L, Meurisse A, Fein F, et al. Overall survival prediction and usefulness of second-line chemotherapy in advanced pancreatic adenocarcinoma. J Natl Cancer Inst 2017;109. doi: 10.1093/jnci/djx037.
17. Hsu CC, Liu KH, Chang PH, Chen PT, Hung CY, Hsueh SW, et al. Development and validation of a prognostic nomogram to predict survival in patients with advanced pancreatic cancer receiving second-line palliative chemotherapy. J Gastroenterol Hepatol 2020;35:1694–703.
18. Lee JE, Lee HS, Chung MJ, Park JY, Park SW, Song SY, et al. Analysis of clinical predictive factors affecting the outcome of second-line chemotherapy for gemcitabine-refractory advanced pancreatic cancer. Gut Liver 2020;14:135–43.
19. Colloca G. Performance status as prognostic factor in phase III trials of first-line chemotherapy of unresectable or metastatic pancreatic cancer: a trial-level meta-analysis. Asia Pac J Clin Oncol 2021 Jun 23 [Epub]. http://doi.org/10.1111/ajco.13598.
20. Sohal D, Kennedy EB, Khorana A, Copur MS, Crane CH, Garrido-Laguna I, et al. Metastatic pancreatic cancer: ASCO clinical practice guideline update. J Clin Oncol 2018;36:2545–56.
21. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(Suppl 5):v56–68.
22. Kim JH, Lee SC, Oh SY, Song SY, Lee N, Nam EM, et al. Attenuated FOLFIRINOX in the salvage treatment of gemcitabine-refractory advanced pancreatic cancer: a phase II study. Cancer Commun (Lond) 2018;38:32.
23. Portal A, Pernot S, Tougeron D, Arbaud C, Bidault AT, de la Fouchardière C, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after FOLFIRINOX failure: an AGEO prospective multicentre cohort. Br J Cancer 2015;113:989–95.
24. da Rocha Lino A, Abrahão CM, Brandão RM, Gomes JR, Ferrian AM, Machado MC, et al. Role of gemcitabine as second-line therapy after progression on FOLFIRINOX in advanced pancreatic cancer: a retrospective analysis. J Gastrointest Oncol 2015;6:511–5.
25. Viaud J, Brac C, Artru P, Le Pabic E, Leconte B, Bodère A, et al. Gemcitabine as second-line chemotherapy after FOLFIRINOX failure in advanced pancreatic adenocarcinoma: a retrospective study. Dig Liver Dis 2017;49:692–6.
26. Sarabi M, Mais L, Oussaid N, Desseigne F, Guibert P, De La Fouchardiere C. Use of gemcitabine as a second-line treatment following chemotherapy with FOLFIRINOX for metastatic pancreatic adenocarcinoma. Oncol Lett 2017;13:4917–24.

Original article

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):133-140
https://doi.org/10.12701/yujm.2021.01445

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Patient outcomes and prognostic factors associated with colonic perforation surgery: a retrospective study

Do-bin Lee, Seonhui Shin, Chun-Seok Yang

Department of Surgery, Daegu Catholic University Medical Center, Daegu Catholic University School of Medicine, Daegu, Korea

Background: Despite advances in surgery and intensive perioperative care, fecal peritonitis secondary to colonic perforation is associated with high rates of morbidity and mortality. This study was performed to review the outcomes of patients who underwent colonic perforation surgery and to evaluate the prognostic factors associated with mortality.

Methods: A retrospective analysis was performed on 224 consecutive patients who underwent emergency colonic perforation surgery between January 2008 and May 2019. We divided the patients into survivor and non-survivor groups and compared their surgical outcomes.

Results: The most common cause of colon perforation was malignancy in 54 patients (24.1%), followed by iatrogenic perforation in 41 (18.3%), stercoral perforation in 39 (17.4%), and diverticulitis in 37 (16.5%). The sigmoid colon (n=124, 55.4%) was the most common location of perforation, followed by the ascending colon, rectum, and cecum. Forty-five patients (20.1%) died within 1 month after surgery. Comparing the 179 survivors with the 45 non-survivors, the patient characteristics associated with mortality were advanced age, low systolic blood pressure, tachycardia, organ failure, high C-reactive protein, high creatinine, prolonged prothrombin time, and high lactate level. The presence of free or feculent fluid, diffuse peritonitis, and right-sided perforation were associated with mortality. In multivariate analysis, advanced age, organ failure, right-sided perforation, and diffuse peritonitis independently predicted mortality within 1 month after surgery.

Conclusion: Age and organ failure were prognostic factors for mortality associated with colon perforation. Furthermore, right-sided perforation and diffuse peritonitis demonstrated a significant association with patient mortality.

Keywords: Intestinal perforation; Peritonitis; Postoperative complication; Surgical stomas

Introduction

Fecal peritonitis secondary to colonic perforation is a life-threatening condition, and emergency surgical management is associated with high morbidity and mortality rates. Despite advances in surgical techniques and perioperative management, surgical outcomes after colonic perforation have not improved [1-4]. It is important to preoperatively evaluate the severity of peritonitis and identify the associated risk factors for mortality because patients with severe peritonitis require immediate surgical management and high-quality intensive care. Additionally, the severity of the peritonitis, potential predictors, and the likelihood of mortality should be included in the information provided to patients and their families.

Several studies have investigated the prognostic factors associated with the mortality and morbidity of patients with fecal peritonitis; consequently, several scoring systems are available [1,5-7].

Received: August 11, 2021 • **Revised:** September 18, 2021 • **Accepted:** September 28, 2021
Corresponding author: Chun-Seok Yang, MD
Department of Surgery, Daegu Catholic University Medical Center, Daegu Catholic University School of Medicine, 33 Duryugongwon-ro 17-gil, Nam-gu, Daegu 42472, Korea
Tel: +82-53-650-4065 • Fax: +82-53-624-7185 • E-mail: gsyangcs@gmail.com

However, these risk factors and scoring systems have only been validated in small-population studies and are not clinically prevalent. Nonetheless, many studies are ongoing to determine other risk factors associated with mortality in patients who undergo colonic perforation.

Hartmann's procedure is the standard surgical procedure for treating left colonic perforation [8,9]. Hartmann's procedure is associated with low quality of life because of the colostomy care required [10], and restoration of intestinal continuity is associated with morbidity and mortality [11]. The reversal rate of Hartmann's procedure tends to be lower than 50% in most reported articles [12]. However, it is inconclusive whether primary resection and anastomosis without fecal diversion is safer than Hartmann's procedure for left colonic perforation.

Thus, the aim of this observational retrospective study was to review the outcomes of patients who underwent emergency surgery for fecal peritonitis secondary to colonic perforation. The primary objective was to compare various factors between survivors and non-survivors. Accordingly, we aimed to predict outcomes based on patient conditions before and during surgery. The secondary objective was to evaluate the necessity of fecal diversion in patients with left colonic perforation without prognostic factors.

Methods

Ethical statements: The study protocol was approved by the Institutional Review Board (IRB) of Daegu Catholic University Hospital (IRB No: CR-21-069), which waived the need for informed consent due to the retrospective design of the study.

1. Study design and population

For this retrospective study, we selected 224 consecutive patients who underwent emergency surgery for fecal peritonitis secondary to colon perforation between January 2008 and May 2019 at Daegu Catholic University Hospital in Korea. Patients with perforations from other gastrointestinal conditions were excluded.

2. Data collection

Patient clinical and management data were collected from medical chart reviews. This included patient demographics such as sex, age, height, weight, body mass index, comorbidities, time from symptom onset to surgery, American Society of Anesthesiologists (ASA) physical status (PS) classification, initial vital signs, white blood cell count, hemoglobin, prothrombin time, activated partial thromboplastin time, serum protein levels, albumin, lactate, C-reactive protein (CRP), creatinine, and blood urea nitrogen at the time of admission. The surgical and pathological reports were reviewed to obtain data regarding the extent of peritoneal contamination, the types of surgery performed, and the sites and causes of perforation. In addition, the length of operation, perioperative complications, mortality, and length of hospital stay were reviewed. Patients were divided into survivors and non-survivors, and clinical data were compared between the groups.

We defined advanced age as > 70 years. Organ failure was defined as follows: (1) renal failure with creatinine levels of > 1.4 mg/dL, (2) circulatory failure with systolic arterial pressure of < 90 mmHg requiring inotropes, and (3) respiratory failure with partial pressure of oxygen < 60 mmHg. Free fluid was defined as the presence of hypodense fluid within the pelvic cavity, subphrenic space, paracolic gutters, or other intraperitoneal spaces on computed tomography (CT) scan. Feculent fluid was defined as the presence of feces protruding through the perforation site with spillage to the adjacent peritoneal cavity on CT scan. Free perforation was defined as air bubbles or air collection within the abdominal cavity, with a distance greater than 5 cm of the affected bowel segment. Diffuse peritonitis was defined as contamination or exudate in the four quadrants during surgery.

The left colon was defined as the descending colon to the rectum. Perioperative mortality was defined as death occurring within 1 month of surgery. Complications were graded according to the Clavien-Dindo classification [13].

3. Operative parameters

We reported postoperative morbidity and mortality, fecal diversion, specialty of the attending surgeon, and rate of bowel reconstruction. The operation results (Hartmann's procedure, primary resection and anastomosis with or without fecal diversion, anastomotic dehiscence, or stoma closure) were also recorded.

4. Subgroup analysis

In accordance with our second objective, we evaluated the necessity of fecal diversion in patients with left colonic perforation without prognostic factors. Thus, to compare the surgical outcomes with or without fecal diversion, we excluded 106 patients who had diffuse peritonitis from the 165 patients with left colonic perforation because diffuse peritonitis was an independent surgical prognostic factor. Thus, the sub-analysis included a group of patients with left colonic perforation at low risk of mortality. Accordingly, 59 patients were included in the sub-analysis.

5. Statistical methods

Comparisons between groups were performed using the chi-

square test or Student *t*-test. We used two-way contingency tables to compare discrete variables and implemented Fisher exact test when low expected values were present. Univariate and multivariate analyses were performed. The variables were analyzed for various outcomes using simple logistic regression, and odds ratios and 95% confidence intervals were reported. For multivariate analysis, a multiple logistic regression model was used. The Mann-Whitney *U*-test was used to analyze the differences in non-categorical variables among the subgroups. All analyses were performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and all *p*-values were two-sided; *p*-values of < 0.05 were considered statistically significant.

Results

Two hundred and twenty-four patients were included in this study. The patient characteristics are presented in Table 1. The mean patient age was 67.5 ± 15.3 years (102 male, 122 female). The most common perforation site was the sigmoid colon in 124 patients (55.4%); 59 patients (26.3%) had perforations on the right side and 165 (73.7%) had perforations on the left side. Resection and anastomosis (50.0%) were the most frequently performed surgeries, followed by Hartmann's procedure (27.7%). Malignancy was the most common cause of perforation in both groups, but stercoral and ischemic colitis were more common in the non-survivors.

A comparison of the factors associated with survivors and non-survivors indicated that age (66 ± 15.5 years vs. 73.4 ± 13.2 years, $p = 0.004$), organ failure (19.6% vs. 53.3%, $p < 0.001$), systolic blood pressure (117.7 ± 22 mmHg vs. 105.4 ± 30.3 mmHg, $p = 0.003$), and heart rate (87.5 ± 16.1 beats/min vs. 94.5 ± 20.6 beats/min, $p = 0.041$) were significantly different (Table 2). Analysis of laboratory values indicated that CRP, creatinine, prothrombin time, and lactate levels were significantly different between the groups. Analysis of the factors associated with characteristics of peritonitis indicated that free fluid (50.6% vs. 76.7%, $p = 0.003$), feculent fluid (36% vs. 55.6%, $p = 0.027$), diffuse peritonitis (52.6% vs. 82.2%, $p = 0.001$), and right-sided perforation (22.9% vs. 40%, $p = 0.033$) were significantly different. The operative outcomes are summarized in Table 3. There were 89 patients (39.7%) with Clavien-Dindo classification ≥ III, of whom 45 (20.1%) died within 1 month after surgery. Of the total, 120 patients (53.6%) underwent fecal diversions, such as Hartmann's procedure, ileostomy, or colostomy, and 64 (72.7%) of the 88 surviving patients underwent stoma closure.

The univariate and multivariate regression analyses are presented in Table 4. Age of > 70 years, ≥ 2 comorbidities, organ failure, renal failure, prolonged prothrombin time, free fluid, feculent fluid, diffuse peritonitis, and right-sided perforation were associated with mortality. When multivariate analysis was performed to determine whether the aforementioned factors were prognostic, only advanced age, organ failure, right-sided perforation, and diffuse peritonitis were statistically significant.

Sub-analysis between the group that underwent fecal diversion (n = 30) and the group that underwent surgical methods without fecal diversion (n = 29) revealed that there was no significant difference between the groups in terms of preoperative and intraoperative findings such as age and comorbidities. This suggests that there were no preoperative differences in other risk factors for mortality. Moreover, there were nine patients (30.0%) whose stoma could not be reversed. Nonetheless, there was no significant difference in mortality and morbidity between the groups (Table 5).

Discussion

Colonic perforation causes widespread dissemination of bacteria and feces into the intraperitoneal space and can lead to peritonitis, septic shock, and multiple organ failure. The mortality rate associated with colon perforation reportedly ranges from 6.2% to 33.3% [1,5-7,14-17]. Similarly, the mortality rate in our study was 20.1%. Our results also showed that old age, organ failure, right-sided perforation, and diffuse peritonitis were associated with mortality. In addition, in the absence of diffuse peritonitis, even patients with left colon perforations showed comparable surgical outcomes with or without fecal diversion. Thus, considering that there are several complications associated with stoma reversal and that many patients have a permanent stoma, a stoma can be omitted if there are no associated risk factors.

Fecal peritonitis due to colonic perforation is largely associated with mortality due to factors such as patient characteristics (including age, ASA PS classification, concurrent medical disease, immunosuppression, and performance status), peritonitis severity, or an interaction between them. Factors such as organ failure and various deteriorations of the blood represent an interaction between patient characteristics and peritonitis severity. Moreover, there are reports of worsening prognosis in patients with lactic acidosis, leukopenia, and bleeding tendency [9,18,19].

In a large cohort of patients with fecal peritonitis, the strongest independent risk factors for mortality were increased age, renal dysfunction, hypothermia, and low hematocrit levels [20]. Furthermore, Tan et al. [21] showed that there was a significant association between mortality and morbidity rates and ASA PS classification, as well as the acute physiology component of the Acute Physiology and Chronic Health Evaluation II score in patients

Table 1. Characteristics of the study population and comparison between the survivors and non-survivors

Characteristic	Overall	Survivor	Non-survivor	*p*-value
No. of patients	224	179	45	
Sex				>0.999
Male	102 (45.5)	82 (45.8)	20 (44.4)	
Female	122 (54.5)	97 (54.2)	25 (55.6)	
Age (yr)	67.5±15.3	66.0 ± 15.5	73.4 ± 13.2	0.004
ASA PS classification				0.118
I	52 (23.2)	47 (26.3)	5 (11.1)	
II	119 (53.1)	94 (52.5)	25 (55.6)	
III	49 (21.9)	35 (19.6)	14 (31.1)	
IV	4 (1.8)	3 (1.7)	1 (2.2)	
Location				0.160
Cecum	18 (8.0)	14 (7.8)	4 (8.9)	
Ascending colon	22 (9.8)	16 (8.9)	6 (13.3)	
Hepatic flexure colon	3 (1.3)	2 (1.1)	1 (2.2)	
Transverse colon	16 (7.1)	8 (4.5)	7 (15.6)	
Splenic flexure colon	5 (2.2)	4 (2.2)	2 (4.4)	
Descending colon	15 (6.7)	12 (6.7)	3 (6.7)	
Sigmoid colon	124 (55.4)	105 (58.7)	19 (42.2)	
Rectum	21 (9.4)	18 (10.1)	3 (6.7)	
Sidedness				0.033
Right location	59 (26.3)	41 (22.9)	18 (40.0)	
Left location	165 (73.7)	138 (77.1)	27 (60.0)	
Types of surgery				0.004
Hartmann's operation	62 (27.7)	41 (22.9)	21 (46.7)	
Resection and anastomosis	112 (50)	93 (52)	19 (42.2)	
Primary closure	35 (15.6)	33 (18.4)	2 (4.4)	
Stoma only	11 (4.9)	10 (5.6)	1 (2.2)	
Drainage only	4 (1.8)	2 (1.1)	2 (4.4)	
Stoma creation	120 (53.6)	88 (49.2)	32 (71.1)	0.013
No stoma creation	104 (46.4)	91 (50.8)	13 (28.9)	
Causes of perforation				0.023
Malignancy	54 (24.1)	41 (22.9)	13 (28.9)	
Diverticulitis	37 (16.5)	30 (16.8)	7 (15.6)	
Iatrogenic	41 (18.3)	39 (21.8)	2 (4.4)	
Ischemic colitis	16 (7.1)	9 (5.0)	7 (15.6)	
Stercoral	39 (17.4)	28 (15.6)	11 (24.4)	
Trauma	24 (10.7)	21 (11.7)	3 (6.7)	
Unknown	13 (5.8)	11 (6.1)	2 (4.4)	

Values are presented as number only, number (%), or mean±standard deviation.
ASA, American Society of Anesthesiologists; PS, physical status.

with colon cancer perforation. These findings are further supported by those of Yoo et al. [22]. Thus, a scoring system is useful for objectively describing patient conditions, thereby aiding surgical decisions for patients with fecal peritonitis [5].

While the predictive value of factors that reflect the severity of peritonitis has been previously studied, it is difficult to quantitatively measure the degree of peritonitis. Until now, only a scoring system based on the peritonitis scope and spillage content has been developed. Nevertheless, these studies emphasize the importance of diffuse peritonitis. There are reports that the spread of ascites on a preoperative CT scan is significant for predicting mortality [18]. Similarly, we showed that prognosis was not affected by the degree of contamination of the ascites, but rather the extent to which it had spread. These results support the speculation that the

Table 2. Comparison of perioperative factors between the survivors and non-survivors

Characteristic	Survivor (n = 179)	Non-survivor (n = 45)	*p*-value
Time from symptom onset to surgery (day)	1.6 ± 2.7	2.2 ± 3.6	0.251
Organ failure	35 (19.6)	24 (53.3)	< 0.001
Systolic blood pressure (mmHg)	117.7 ± 22	105.4 ± 30.3	0.003
Heart rate (beats/min)	87.5 ± 16.1	94.5 ± 20.6	0.041
White blood cell count (10^3/μL)			0.178
< 4.0	30 (16.8)	13 (28.9)	
≥ 4.0, < 10.0	73 (40.8)	15 (33.3)	
≥ 10.0	76 (42.5)	17 (37.8)	
C-reactive protein (mg/L)	89.7 ± 104.4	135.2 ± 119.1	0.029
Creatinine (mg/dL)	1.1 ± 1.1	1.4 ± 0.9	0.037
Prothrombin time (sec)	14.4 ± 1.4	16.3 ± 3.1	< 0.001
Lactate (mmol/L)	2.8 ± 1.9	5.5 ± 2.4	0.001
Free perforation	142 (81.1)	40 (88.9)	0.315
Free fluid	88 (50.6)	33 (76.7)	0.003
Feculent fluid	63 (36.0)	25 (55.6)	0.027
Abscess	23 (13.1)	4 (9.3)	0.670
Diffuse peritonitis	92 (52.6)	37 (82.2)	0.001
Retroperitoneal perforation	25 (14.3)	7 (15.9)	0.973

Values are presented as mean ± standard deviation or number (%).

Table 3. Comparison of operative outcomes between the survivors and non-survivors

Characteristic	Survivor (n = 179)	Non-survivor (n = 45)	*p*-value
Colorectal surgeon	137 (76.5)	30 (66.7)	0.243
Operative time (min)	169.5 ± 67.1	186.2 ± 131.1	0.235
Intraoperative lavage	14 (7.8)	2 (4.4)	0.745
Stoma reversal	64 (72.7)[a]		NA
Complication			
Surgical site infection	47 (26.3)	10 (22.2)	0.716
Intraabdominal abscess	36 (20.1)	8 (17.8)	0.887
Septic shock	9 (5.0)	40 (88.9)	< 0.001
Pneumonia	19 (10.6)	8 (17.8)	0.288
Cardiovascular events	3 (1.7)	13 (28.9)	< 0.001
Paralytic ileus	8 (4.5)	0 (0)	0.363
Anastomosis leakage	2 (1.1)	6 (13.3)	0.001
Multiorgan failure	1 (0.6)	39 (86.7)	< 0.001
Clavien-Dindo classification			NA
I	19 (10.6)		
II	58 (32.4)		
III	38 (21.2)		
IV	6 (3.4)		

Values are presented as number (%) or mean ± standard deviation.
NA, not applicable.
[a]The stoma reversal rate was based on 88 survivors among patients with stoma creation.

spread of ascites indicates the severity of peritonitis or the duration from the onset of perforation. While mortality rates have been shown to increase with the interval length between the time of hollow organ perforation and the time of surgery [23], our results did not reveal interval length as a prognostic factor for mortality.

Furthermore, our result that diffuse peritonitis is an important prognostic factor is similar to results from studies on colorectal cancer obstruction. When perforation occurs proximal to the ob-

Table 4. Analysis of mortality

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age (yr)				
≤70	1			
>70	3.496 (1.667–7.331)	0.001	2.993 (1.254–7.139)	0.013
Comorbidity, ≥2	3.032 (1.549–5.934)	0.001	1.738 (0.767–3.938)	0.185
Organ failure	4.702 (2.353–9.397)	<0.001	4.207 (1.326–13.347)	0.015
Renal failure	3.568 (1.663–7.658)	0.001	0.606 (0.168–2.189)	0.445
Prolonged prothrombin time (>15 sec)	3.225 (1.646–6.319)	0.001	1.899 (0.855–4.219)	0.115
Free fluid	3.225 (1.497–6.947)	0.003	1.404 (0.542–3.633)	0.485
Feculent fluid	2.222 (1.144–4.317)	0.018	0.935 (0.39–2.245)	0.881
Diffuse peritonitis	4.173 (1.838–9.472)	0.001	3.184 (1.208–8.397)	0.019
Sidedness				
Right location	2.244 (1.125–4.477)	0.022	2.348 (1.026–5.373)	0.043
Left location	1			

CI, confidence interval.

Table 5. Subgroup analysis of patients with left-sided colon perforation and low risk factors

Characteristic	Without fecal diversion (n=29)	With fecal diversion (n=30)	*p*-value
Sex			0.908
Male	13 (44.8)	13 (43.3)	
Female	16 (55.2)	17 (56.7)	
Age (yr)	62.5±16.3	65.4±16.3	0.299
Systolic blood pressure (mmHg)	124.7±14.5	119.2±19.2	0.114
Heart rate (beats/min)	85.6±14.4	88.5±12.4	0.346
C-reactive protein (mg/L)	51.9±71.2	85.2±88.7	0.115
Creatinine (mg/dL)	0.7±0.2	0.8±0.3	0.169
Prothrombin time (s)	13.7±0.8	14.1±1.1	0.179
Lactate (mmol/L)	2.2±1.0	1.7±0.6	0.402
Free perforation	22 (78.6)	19 (65.5)	0.273
Free fluid	10 (35.7)	9 (31.0)	0.708
Feculent fluid	6 (21.4)	8 (27.6)	0.589
Abscess	6 (21.4)	5 (17.2)	0.689
Retroperitoneal perforation	6 (21.4)	4 (13.8)	0.504[a]
Operative time (min)	166.2±59.5	185.1±63.6	0.180
Hospital stay (day)	13.9±6.1	20.1±12.1	0.050
Clavien-Dindo classification			0.543
I	1 (3.4)	3 (10.0)	
II	10 (34.5)	7 (23.3)	
III	10 (34.5)	7 (23.3)	
IV	5 (17.2)	7 (23.3)	
Mortality	2 (6.9)	2 (6.7)	>0.999[a]

Values are presented as number (%) or mean±standard deviation.
[a]Statistical significance was assessed by Fisher exact test.

structing tumor, it tends to be severe due to intestinal distension, and peritoneal contamination is diffuse and fecal. This leads to severe septic shock, which increases the risk of perioperative mortality. In contrast, when perforation occurs at the cancer site, the contamination is usually localized, typically leading to purulent collection and resulting in a lower risk of severe peritonitis [24]. In our

study, this is also the reason that peritonitis on the right side had a worse prognosis than that on the left side. In cases of perforation on the right side, more diffuse peritonitis occurred, which led to a worse prognosis.

The optimal surgical treatment for colonic perforation remains controversial, and the treatment strategy depends on the patient's general condition and the experience of the primary surgeon. Despite advancements in surgical techniques, Hartmann's procedure is still frequently performed to treat left colonic perforation [8,9]. The literature that primary anastomosis has comparable surgical outcomes to Hartmann's procedure has mainly been studied in patients with diverticular perforation [25]. Primary anastomosis without fecal diversion has a longer operative time, and Hartmann's procedure is a safer option for patients with severe medical illness. Therefore, it is important to determine the patient's overall condition and account for risk factors and conditions that are associated with mortality prior to surgery. In the absence of diffuse peritonitis, primary anastomosis and stoma omission had similar operative outcomes to Hartmann's procedure even in patients with left colon perforation.

Our study has some limitations. First, this was a single-center study, and we could not proceed with the validation process. Second, our study had a retrospective design; thus, we could not obtain some patient information, such as CRP and lactate levels. Third, because this study included patients who underwent surgery, there may be limitations in the clinical course of fecal peritonitis. Finally, the surgeries were performed by 10 different surgeons, which may have led to inconsistent quality. However, there was no significant difference in the postoperative outcomes based on the surgeon's specialty.

In conclusion, advanced age, organ failure, right-sided perforation, and diffuse peritonitis were found to be prognostic factors for colon perforation accompanied by fecal peritonitis. Thus, these findings demonstrate that it is important to determine the type of surgery, extent of resection, and whether fecal diversion should be performed.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization, Data curation: all authors; Investigation: DL, SS; Formal analysis, Project administration, Software, Supervision, Validation: CSY; Methodology: SS, CSY; Writing-original draft: DL; Writing-review & editing: CSY.

ORCID

Do-bin Lee, https://orcid.org/0000-0002-7249-7074
Seonhui Shin, https://orcid.org/0000-0003-4676-9037
Chun-Seok Yang, https://orcid.org/0000-0002-5527-6819

References

1. Bielecki K, Kamiński P, Klukowski M. Large bowel perforation: morbidity and mortality. Tech Coloproctol 2002;6:177–82.
2. Tridente A, Bion J, Mills GH, Gordon AC, Clarke GM, Walden A, et al. Derivation and validation of a prognostic model for postoperative risk stratification of critically ill patients with faecal peritonitis. Ann Intensive Care 2017;7:96.
3. Biondo S, Kreisler E, Millan M, Fraccalvieri D, Golda T, Martí Ragué J, et al. Differences in patient postoperative and long-term outcomes between obstructive and perforated colonic cancer. Am J Surg 2008;195:427–32.
4. Lee IK, Sung NY, Lee YS, Lee SC, Kang WK, Cho HM, et al. The survival rate and prognostic factors in 26 perforated colorectal cancer patients. Int J Colorectal Dis 2007;22:467–73.
5. Biondo S, Ramos E, Deiros M, Ragué JM, De Oca J, Moreno P, et al. Prognostic factors for mortality in left colonic peritonitis: a new scoring system. J Am Coll Surg 2000;191:635–42.
6. Shinkawa H, Yasuhara H, Naka S, Yanagie H, Nojiri T, Furuya Y, et al. Factors affecting the early mortality of patients with non-traumatic colorectal perforation. Surg Today 2003;33:13–7.
7. Horiuchi A, Watanabe Y, Doi T, Sato K, Yukumi S, Yoshida M, et al. Evaluation of prognostic factors and scoring system in colonic perforation. World J Gastroenterol 2007;13:3228–31.
8. Cirocchi R, Trastulli S, Desiderio J, Listorti C, Boselli C, Parisi A, et al. Treatment of Hinchey stage III-IV diverticulitis: a systematic review and meta-analysis. Int J Colorectal Dis 2013;28:447–57.
9. Joo Y, Lee Y, Yoo T, Kim J, Park I, Gwak G, et al. Prognostic factors and management for left colonic perforation: can Hartmann's procedure be preventable? Ann Coloproctol 2020;36:178–85.
10. Vermeulen J, Gosselink MP, Busschbach JJ, Lange JF. Avoiding or reversing Hartmann's procedure provides improved quality of life after perforated diverticulitis. J Gastrointest Surg 2010;14:651–7.
11. Richards CH, Roxburgh CS; Scottish Surgical Research Group (SSRG). Surgical outcome in patients undergoing reversal of

Hartmann's procedures: a multicentre study. Colorectal Dis 2015;17:242–9.
12. Horesh N, Rudnicki Y, Dreznik Y, Zbar AP, Gutman M, Zmora O, et al. Reversal of Hartmann's procedure: still a complicated operation. Tech Coloproctol 2018;22:81–7.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
14. Sugimoto K, Sato K, Maekawa H, Sakurada M, Orita H, Ito T, et al. Analysis of the efficacy of direct hemoperfusion with polymyxin B-immobilized fiber (PMX-DHP) according to the prognostic factors in patients with colorectal perforation. Surg Today 2013;43:1031–8.
15. Alvarez JA, Baldonedo RF, Bear IG, Otero J, Pire G, Alvarez P, et al. Outcome and prognostic factors of morbidity and mortality in perforated sigmoid diverticulitis. Int Surg 2009;94:240–8.
16. Komatsu S, Shimomatsuya T, Nakajima M, Amaya H, Kobuchi T, Shiraishi S, et al. Prognostic factors and scoring system for survival in colonic perforation. Hepatogastroenterology 2005;52:761–4.
17. Kriwanek S, Armbruster C, Beckerhinn P, Dittrich K. Prognostic factors for survival in colonic perforation. Int J Colorectal Dis 1994;9:158–62.
18. Nakamura F, Yui R, Muratsu A, Sakuramoto K, Muroya T, Ikegawa H, et al. Study of the prognostic factor of the colon perforation case with the pan-peritonitis that needed emergency surgery: a single-center observational study. Acute Med Surg 2019;6:379–84.
19. Jobin SP, Maitra S, Baidya DK, Subramaniam R, Prasad G, Seenu V. Role of serial lactate measurement to predict 28-day mortality in patients undergoing emergency laparotomy for perforation peritonitis: prospective observational study. J Intensive Care 2019;7:58.
20. Tridente A, Clarke GM, Walden A, McKechnie S, Hutton P, Mills GH, et al. Patients with faecal peritonitis admitted to European intensive care units: an epidemiological survey of the GenOSept cohort. Intensive Care Med 2014;40:202–10.
21. Tan KK, Hong CC, Zhang J, Liu JZ, Sim R. Surgery for perforated colorectal malignancy in an Asian population: an institution's experience over 5 years. Int J Colorectal Dis 2010;25:989–95.
22. Yoo RN, Kye BH, Kim G, Kim HJ, Cho HM. Mortality risk factor analysis in colonic perforation: would retroperitoneal contamination increase mortality in colonic perforation? Ann Surg Treat Res 2017;93:203–8.
23. Strobel O, Werner J, Büchler MW. Surgical therapy of peritonitis. Chirurg 2011;82:242–8.
24. Otani K, Kawai K, Hata K, Tanaka T, Nishikawa T, Sasaki K, et al. Colon cancer with perforation. Surg Today 2019;49:15–20.
25. Halim H, Askari A, Nunn R, Hollingshead J. Primary resection anastomosis versus Hartmann's procedure in Hinchey III and IV diverticulitis. World J Emerg Surg 2019;14:32.

Original article

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):141-149
https://doi.org/10.12701/yujm.2021.01571

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Clinical implication of adjuvant chemotherapy according to mismatch repair status in patients with intermediate-risk stage II colon cancer: a retrospective study

Byung Woog Kang[1], Dong Won Baek[1], Eunhye Chang[2], Hye Jin Kim[3], Su Yeon Park[3], Jun Seok Park[3], Gyu Seog Choi[3], Jin Ho Baek[1,*], Jong Gwang Kim[1,*]

[1]Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, Kyungpook National University Cancer Research Institute, School of Medicine, Kyungpook National University, Daegu, Korea
[2]Department of Internal Medicine, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[3]Department of Surgery, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea

Background: The present study evaluated the clinical implications of adjuvant chemotherapy according to the mismatch repair (MMR) status and clinicopathologic features of patients with intermediate- and high-risk stage II colon cancer (CC).
Methods: This study retrospectively reviewed 5,774 patients who were diagnosed with CC and underwent curative surgical resection at Kyungpook National University Chilgok Hospital. The patients were enrolled according to the following criteria: (1) pathologically diagnosed with primary CC; (2) stage II CC classified based on the 7th edition of the American Joint Committee on Cancer staging system; (3) intermediate- and high-risk features; and (4) available test results for MMR status. A total of 286 patients met these criteria and were included in the study.
Results: Among the 286 patients, 54 (18.9%) were identified as microsatellite instability-high (MSI-H) or deficient MMR (dMMR). Although all the patients identified as MSI-H/dMMR showed better survival outcomes, T4 tumors and adjuvant chemotherapy were identified as independent prognostic factors for survival. For the intermediate-risk patients identified as MSI-low (MSI-L)/microsatellite stable (MSS) or proficient MMR (pMMR), adjuvant chemotherapy exhibited a significantly better disease-free survival (DFS) but had no impact on overall survival (OS). Oxaliplatin-containing regimens showed no association with DFS or OS. Adjuvant chemotherapy was not associated with DFS in intermediate-risk patients identified as MSI-H/dMMR.
Conclusion: The current study found that the use of adjuvant chemotherapy was correlated with better DFS in MSI-L/MSS or pMMR intermediate-risk stage II CC patients.

Keywords: Adjuvant chemotherapy; Colonic neoplasms; DNA mismatch repair; Intermediate risk; Stage II disease

Received: October 20, 2021 • **Revised:** November 20, 2021 • **Accepted:** November 20, 2021

Corresponding author: Jin Ho Baek, MD, PhD
Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, Kyungpook National University Cancer Research Institute, School of Medicine, Kyungpook National University, 807 Hoguk-ro, Buk-gu, Daegu 41404, Korea
Tel: +82-53-200-2674 • Fax: +82-53-200-2029 • E-mail: jhbaek@knu.ac.kr

Jong Gwang Kim, MD, PhD
Department of Oncology/Hematology, Kyungpook National University Chilgok Hospital, Kyungpook National University Cancer Research Institute, School of Medicine, Kyungpook National University, 807 Hoguk-ro, Buk-gu, Daegu 41404, Korea
Tel: +82-53-200-2623 • Fax: +82-53-200-2029 • E-mail: jkk21c@knu.ac.kr

*These authors have contributed equally to this work as corresponding authors.

Introduction

Complete surgical resection followed by adjuvant chemotherapy according to pathologic stage is the current standard of care for patients with locoregional colon cancer (CC). For patients with stage III disease, the standard adjuvant chemotherapy is usually FOLFOX (infusional 5-fluorouracil [5-FU], leucovorin, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) [1,2]. However, for patients with stage II disease, the additional survival benefit from adjuvant chemotherapy varies according to clinicopathological parameters, including microsatellite instability (MSI). Thus, standard guidelines do not recommend adjuvant therapy for patients with low-risk stage II disease, while recommending adjuvant chemotherapy for patients with high-risk stage II disease (T3N0 with high-risk factor for recurrence or T4N0). High-risk factors include poorly differentiated histology, lymphovascular invasion, perineural invasion, bowel obstruction, perforation, positive margin, and inadequately sampled lymph nodes, according to National Comprehensive Cancer Network (NCCN) guidelines [3-6].

MSI, the abnormal shortening or lengthening of DNA by 1–6 repeating base pair units, results from the inactivation of the DNA mismatch repair (MMR) system and is found in approximately 15% of CCs [7]. Thus, MMR status is an important factor to consider when deciding whether to use adjuvant chemotherapy in patients with stage II CC [8]. According to previous studies, CC patients with MSI-high (MSI-H) tumors have a more favorable prognosis than those with microsatellite stable (MSS) tumors [9-11]. In addition, patients with MSI-low (MSI-L) or MSS tumors exhibited improved outcomes with 5-FU-based adjuvant chemotherapy, while adjuvant treatment was seemingly detrimental for patients with MSI-H stage II CC [10].

Recently, the European Society for Medical Oncology (ESMO) subdivided high-risk stage II CC into high-risk (T4, < 12 lymph nodes or multiple risk factors) and intermediate-risk (lymphatic invasion, perineural invasion, vascular invasion, histologic grade 3, obstruction, or carcinoembryonic antigen [CEA] > 5 ng/mL) groups. In addition, they recommended adjuvant FOLFOX or CAPOX for high-risk stage II CC regardless of MMR status and 5-FU or capecitabine chemotherapy alone for intermediate-risk stage II CC with MSS [12]. However, there are discrepancies in the chemotherapy recommendations for high- and intermediate-risk stage II CC between the ESMO and NCCN guidelines [6].

Accordingly, the present study evaluated the clinical implications of adjuvant chemotherapy for high-risk and intermediate-risk stage II CC according to the NCCN and ESMO guidelines. We also investigated the prognostic impact of clinicopathologic features, including MSI status, in patients with stage II CC.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Chilgok Hospital (IRB No: 2017-11-009), and the requirement for informed consent was waived.

1. Patients and treatment

This study retrospectively reviewed 5,774 patients who were diagnosed with CC and underwent curative surgical resection at Kyungpook National University Chilgok Hospital between January 2011 and December 2019. The patients were enrolled according to the following criteria: (1) pathologically diagnosed with primary CC; (2) stage II CC based on the 7th edition of the American Joint Committee on Cancer staging system [13]; (3) intermediate- and high-risk features [12]; and (4) available test results for MMR status. A total of 286 patients met all of these criteria and were included in the study (Fig. 1). Patient records were also reviewed for data on their medical history, age, sex, adjuvant chemotherapy regimen, surgical methods, and pathologic results.

Adjuvant chemotherapy was started 3 to 6 weeks after surgery. In the case of capecitabine monotherapy (capecitabine of 1,250 mg/m^2 twice a day, day [D] 1–D14) and CAPOX therapy (oxaliplatin of 130 mg/m^2, D1 and capecitabine of 1,000 mg/m^2 twice a day, D1–D14), the patients received chemotherapy every 3 weeks for 24 weeks [14,15]. In the case of FOLFOX therapy (oxaliplatin of 85 mg/m^2, D1; leucovorin of 400 mg/m^2, D1; 5-FU of 400 mg/m^2 bolus, D1; and 5-FU of 2,400 mg/m^2 continuous, D1–D2), the patients received 12 cycles of chemotherapy every 2 weeks [16,17]. The 5-FU/leucovorin regimen (5-FU of 425 mg/m^2 and leucovorin of 20 mg/m^2, D1–D5) was administered every 4 weeks for six cycles. Dose modifications were performed according to predefined guidelines based on toxicity responses [18]. Observation without adjuvant therapy was also an option for patients who were elderly or patients with an Eastern Cooperative Oncology Group performance status of ≥ 3.

2. Definition of high-risk stage II disease by National Comprehensive Cancer Network guidelines

For patients with MSS, stage II disease was classified as high risk if they exhibited at least one of the poor prognosis features, while all patients with MSI-H were excluded from the high-risk group [6].

3. Definition of intermediate- and high-risk stage II disease by European Society for Medical Oncology guidelines

Patients with stage II disease were classified as intermediate risk if

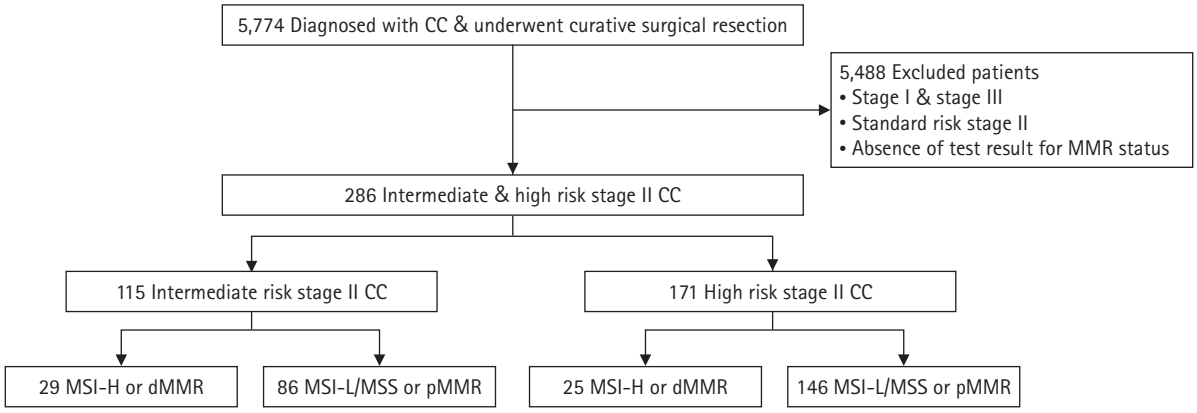

Fig. 1. Flow diagram of patient selection. CC, colon cancer; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, MSI-high; dMMR, deficient MMR; MSI-L, MSI-low; MSS, microsatellite stable; pMMR, proficient MMR.

they exhibited one of the poor prognosis features except for a T4 tumor or inadequately sampled lymph nodes (< 12 lymph nodes). Patients with stage II disease were classified as high risk if they exhibited a T4 tumor, including perforation and/or inadequately sampled lymph nodes or several intermediate-risk factors [12].

4. Determination of mismatch repair status

MSI was evaluated based on immunohistochemistry (IHC) analysis of the expression of MMR proteins (MLH1, MSH2, MSH6, and PMS2) or by molecular MSI testing based on a polymerase chain reaction (PCR) assay [19]. IHC for MMR protein expression was performed on whole sections using an automatic immunostainer (BenchMark XT, Ventana Medical Systems, Tucson, AZ, USA) according to the manufacturer's instructions. Primary monoclonal antibodies against MLH1 (clone M1, prediluted, Ventana Medical Systems), MSH2 (clone G219, 1:100, Cellmark, Rocklin, CA, USA), MSH6 (clone 44, prediluted, Ventana Medical Systems), and PMS2 (clone mrq-28, 1:200, Cellmark), and an ultraView Universal DAB kit (Ventana Medical Systems) were applied to 4-μm-thick 10% formalin-fixed tissue sections. Tumors displaying loss of expression of one or more MMR proteins were considered deficient MMR (dMMR), whereas those with intact MMR proteins were classified as proficient MMR (pMMR). Meanwhile, molecular MSI testing used a panel consisting of five markers (D5S346, BAT26, BST25, D17S250, and D2S123). The amplified PCR products were analyzed using a Model 3500×L Genetic Analyzer (Thermo Fisher Scientific, Seoul, Korea). A locus was determined to be unstable if unequivocal instabilities were observed in the tumor sample in comparison with paired normal DNA from the same patient. The MSI was graded as high (MSI-H) when two or more markers were unstable, low (MSI-L) when one marker was unstable, and stable (MSS) when all markers were stable.

5. Statistical analysis

Descriptive statistics are reported as proportions and medians. Categorical variables were evaluated using chi-square and Fisher exact tests, as appropriate. Disease-free survival (DFS) was measured from the date of surgery to the date of tumor recurrence or all-cause mortality. Overall survival (OS) was calculated from the date of surgery to that of all-cause mortality. Data were censored if patients were free of recurrence or were alive at the last follow-up. The Kaplan-Meier method was used to estimate DFS and OS. The survival curves were compared using a log-rank test according to MMR status or adjuvant chemotherapy. Multivariate survival analyses were performed using the Cox proportional hazard regression model. The hazard ratio and 95% confidence interval were estimated for each factor. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS ver. 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

1. Patient and tumor characteristics

The patient and tumor characteristics are summarized in Table 1. The median age was 70 years (range, 25–88 years) at the time of diagnosis, and 153 patients (53.5%) were male. According to the MMR status results, 54 patients (18.9%) were identified as MSI-H/dMMR. The primary tumors were located in the ascending colon in 100 patients (35.0%), transverse colon in 56 patients (19.6%), and descending colon in 130 patients (45.5%). Right-sided CC was observed in 147 patients (51.4%), and left-sided CC was observed in 139 patients (48.6%). The frequencies of intermediate- and high-risk features were as follows: T4 tumor (n = 51,

Table 1. Patient characteristics

Characteristic	Total	MMR status		*p*-value
		MSI-H/dMMR	MSI-L/MSS or pMMR	
No. of patients	286 (100)	54 (18.9)	232 (81.1)	
Age	70 (25–88)	71 (40–86)	70 (25–88)	0.747
Sex				0.139
Male	153 (53.5)	24 (15.7)	129 (84.3)	
Female	133 (46.5)	30 (22.6)	103 (77.4)	
Primary tumor location				< 0.001
Ascending colon	100 (35.0)	30 (30.0)	70 (70.0)	
Transverse colon	56 (19.6)	13 (23.2)	43 (76.8)	
Descending colon	130 (45.5)	11 (8.5)	119 (91.5)	
Primary tumor sidedness				< 0.001
Right	147 (51.4)	41 (27.9)	106 (72.1)	
Left	139 (48.6)	13 (9.4)	126 (90.6)	
T stage				0.299
T4	51 (17.8)	7 (13.7)	44 (86.3)	
T3	235 (82.2)	47 (20.0)	188 (80.0)	
No. of sampled LNs				0.245
< 12	28 (9.8)	3 (10.7)	25 (89.3)	
≥ 12	258 (90.2)	51 (19.8)	207 (80.2)	
Obstruction				0.579
Yes	22 (7.7)	5 (22.7)	17 (77.3)	
No	264 (92.3)	49 (18.6)	215 (81.4)	
Perforation				> 0.999
Yes	3 (1.0)	0 (0)	3 (100)	
No	283 (99.0)	54 (19.1)	229 (80.9)	
Positive margins				
Yes	0 (0)	0 (0)	0 (0)	
No	286 (100)	54 (18.9)	232 (81.1)	
High-grade tumor				0.002
Yes	25 (8.7)	11 (44.0)	14 (56.0)	
No	261 (91.3)	43 (16.5)	218 (83.5)	
Perineural invasion				0.900
Yes	162 (56.6)	31 (19.1)	131 (80.9)	
No	124 (43.4)	23 (18.5)	101 (81.5)	
Lymphovascular invasion				0.935
Yes	184 (64.3)	35 (19.0)	149 (81.0)	
No	102 (35.7)	19 (18.6)	83 (81.4)	
ESMO guidelines				0.025
Intermediate risk	115 (40.2)	29 (25.2)	86 (74.8)	
High risk	171 (59.8)	25 (14.6)	146 (85.4)	
Adjuvant chemotherapy				0.753
Yes	201 (70.3)	37 (18.4)	164 (81.6)	
No	85 (29.7)	17 (20.0)	68 (80.0)	
Oxaliplatin-contained				0.281
Yes	98 (48.8)	21 (21.4)	77 (78.6)	
No	103 (51.2)	16 (15.5)	87 (84.5)	
Relapse				0.053
Yes	32 (11.2)	2 (6.3)	30 (93.8)	
No	254 (88.8)	52 (20.5)	202 (79.5)	
Death				0.140
Yes	19 (6.6)	1 (5.3)	18 (94.7)	
No	267 (93.4)	53 (19.9)	214 (80.1)	

Values are presented as number (%) or median (range).
MMR, mismatch repair; MSI, microsatellite instability; MSI-H, MSI-high; dMMR, deficient MMR; MSI-L, MSI-low; MSS, microsatellite stable; pMMR, proficient MMR; LN, lymph node; ESMO, European Society for Medical Oncology.

 https://doi.org/10.12701/yujm.2021.01571

17.8%), fewer than 12 lymph nodes examined (n=28, 9.8%), obstruction (n=22, 7.7%), perforation (n=3, 1.0%), high-grade tumor (n=25, 8.7%), perineural invasion (n=162, 56.6%), and lymphovascular invasion (n=184, 64.3%). Among the 286 eligible patients, 201 (70.3%) received adjuvant therapy. Among these 201 patients, 99 (49.3%) received capecitabine alone, four (2.0%) received 5-FU/leucovorin, 95 (47.3%) received FOLFOX, and three (1.5%) received CAPOX as adjuvant chemotherapy. Among the 86 patients with intermediate-risk and MSI-L/MSS or pMMR, 53 (61.6%) received adjuvant therapy. Among these 53 patients, 28 (52.8%) received either capecitabine alone or 5-FU/leucovorin in combination, and 25 (47.2%) received either FOLFOX or CAPOX as adjuvant chemotherapy. The incidence of MSI-H/dMMR was higher with right-sided CC (n=41, 27.9%) and high-grade tumors (n=11, 44.0%).

2. Survival outcomes

With a median follow-up duration of 36.0 months (range, 0.5–105.2 months), the estimated 3-year DFS and OS rates were 88.9% and 93.8%, respectively. During the analyses, 32 patients (11.2%) experienced disease relapse, and 19 patients (6.6%) died. Among the patients with MSI-H, only two experienced relapse, and only one died. According to ESMO guidelines, 115 patients (40.2%) were classified as intermediate risk and 171 (59.8%) as high risk (Table 1). The incidence of MSI-H/dMMR was higher among intermediate-risk patients (n=29, 25.2%) than among high-risk patients (n=25, 14.6%). For the intermediate-risk patients identified as MSI-L/MSS or pMMR (n=86), seven patients experienced a relapse and three patients died. Only one patients who received capecitabine as adjuvant chemotherapy experienced relapse and death, but none of the patients who received an oxaliplatin-containing regimen as adjuvant chemotherapy experienced either relapse or death. For the intermediate-risk patients identified as MSI-L/MSS or pMMR, adjuvant chemotherapy produced a significantly better DFS ($p=0.002$), yet had no impact on OS ($p=0.176$) (Fig. 2). The oxaliplatin-containing regimens were not associated with DFS or OS (Fig. 3). For the intermediate-risk patients identified as MSI-H/dMMR, only one patients who did not receive adjuvant chemotherapy experienced relapse and adjuvant chemotherapy showed no association with DFS ($p=0.678$) (Fig. 4).

3. Prognostic value of microsatellite instability and factors affecting survival outcomes

In the multivariate analysis including intermediate- and high-risk patients, a T4 tumor and adjuvant chemotherapy were both identified as independent prognostic factors for DFS (Table 2) and OS (Table 3).

Discussion

Accumulating data suggest that MMR status and clinicopathologic features are both important determinants in deciding whether to pursue adjuvant chemotherapy for patients with stage II CC. How-

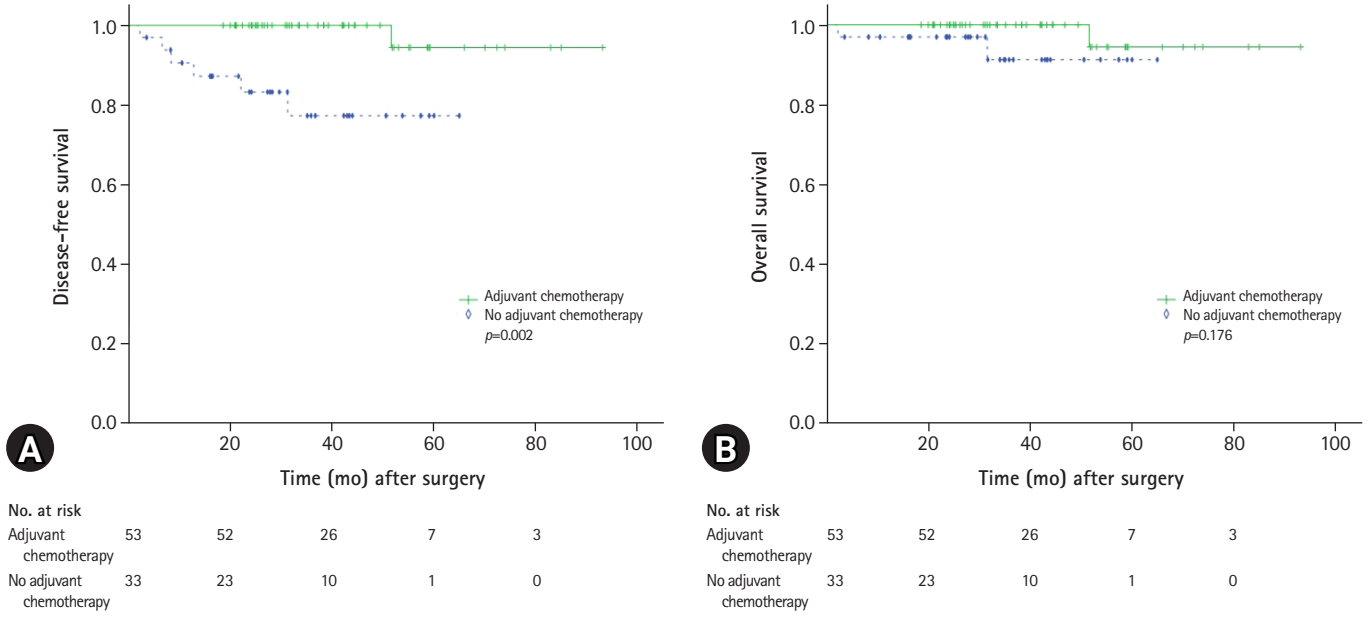

Fig. 2. Kaplan-Meier survival curves for (A) disease-free and (B) overall survival of patients with intermediate-risk stage II colon cancer and microsatellite instability-low/microsatellite stable according to adjuvant chemotherapy.

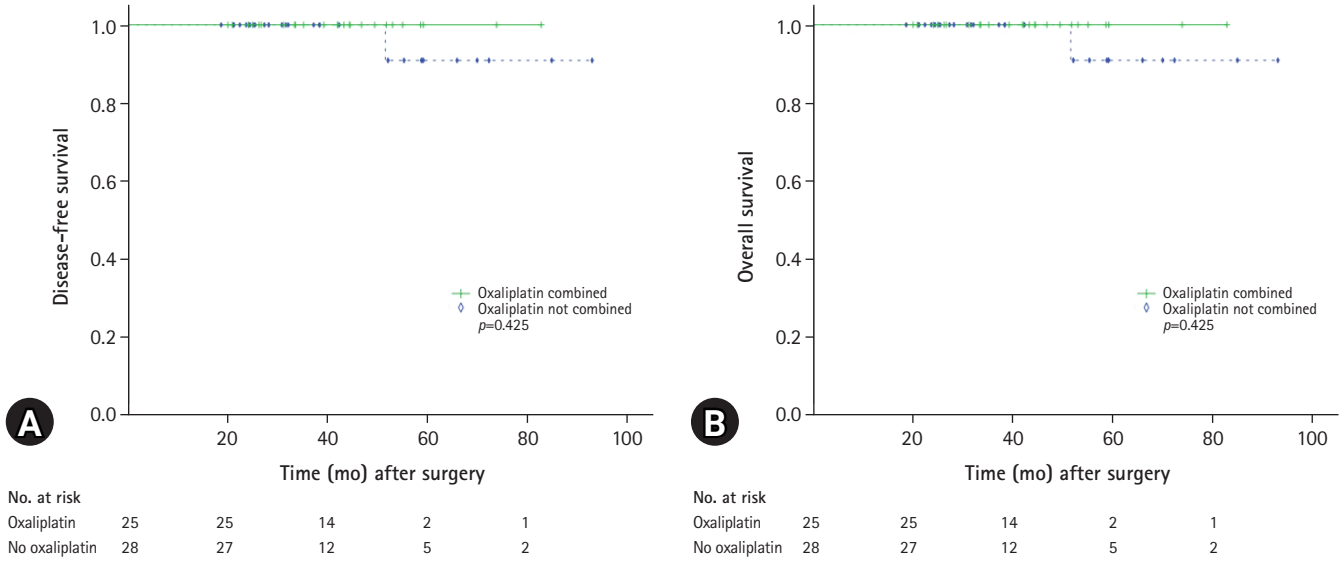

Fig. 3. Kaplan-Meier survival curves for (A) disease-free and (B) overall survival of patients with intermediate-risk stage II colon cancer and microsatellite instability-low/microsatellite stable or proficient mismatch repair according to type of adjuvant chemotherapy.

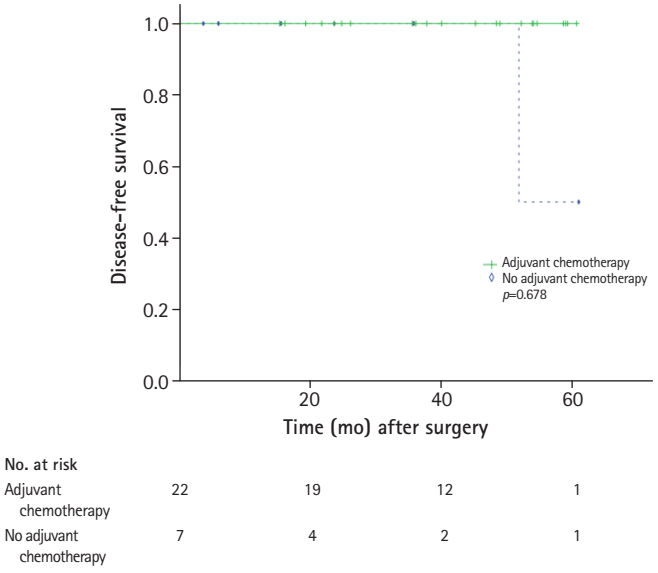

Fig. 4. Kaplan-Meier survival curves for disease-free survival of patients with intermediate-risk stage II colon cancer and microsatellite instability-high or deficient mismatch repair according to adjuvant chemotherapy.

ever, the use of adjuvant chemotherapy in intermediate-risk stage II patients remains debatable. Therefore, the present study investigated the clinical impact of adjuvant chemotherapy in a relatively large cohort of intermediate-risk stage II CC patients. As a result, the intermediate-risk patients identified as MSI-L/MSS or pMMR exhibited improved outcomes with adjuvant chemotherapy, but the addition of oxaliplatin showed no survival benefit. Thus, a further prospective randomized study is needed to explore the benefit of oxaliplatin in adjuvant therapy for MSI-L/MSS or pMMR intermediate-risk stage II patients. Meanwhile, the intermediate-risk patients with tumors identified as MSI-H/dMMR in the present study showed no statistically significant benefit from adjuvant chemotherapy.

Several guidelines suggest that certain clinicopathologic high-risk features may be predictive of benefit from adjuvant chemotherapy for patients with stage II CC [20]. According to NCCN guidelines, high-risk features include T4 tumors; poorly differentiated/undifferentiated histology; lymphovascular invasion; perineural invasion; tumor budding; bowel obstruction; lesions with localized perforations or close, indeterminate, or positive margins; and inadequately sampled lymph nodes (< 12 nodes) [6]. Thus, for high-risk patients, adjuvant therapy can be considered in conjunction with patient/physician discussions personalized for each patient [3,21]. Meanwhile, ESMO guidelines propose both major prognostic parameters (pathological [p] T4 stage including perforations and lymph node sampling < 12) and minor prognostic parameters (high-grade tumor, vascular invasion, lymphatic invasion, perineural invasion, tumor presentation with obstruction, and high preoperative CEA levels) [12]. For intermediate-risk patients (non-MMR/MSI and any risk factor except pT4 or < 12 lymph nodes assessed), 6 months of 5-FU treatment is recommended [12]. However, most studies addressing the role of adjuvant treatment in high-risk stage II settings have been retrospective or unplanned analyses [22]. Moreover, the limitations of these studies are the biologic heterogeneity of the various factors and the lack of an unequivocal definition of clinicopathologic conditions [23].

Table 2. Univariate and multivariate analyses for disease-free survival

Variable	Disease-free survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, ≥65 yr	3.782 (1.325–10.794)	0.013	2.335 (0.795–6.857)	0.123
Male sex	1.120 (0.559–2.262)	0.741	1.016 (0.481–2.146)	0.967
Primary tumor sidedness, right	1.425 (0.708–2.865)	0.321	1.558 (0.727–3.339)	0.255
Tumor stage, T4	4.027 (2.002–8.098)	<0.001	4.679 (2.020–10.838)	<0.001
Sampled LNs, <12	1.715 (0.697–4.219)	0.240	2.053 (0.745–5.658)	0.165
Obstruction, yes	2.268 (0.309–16.667)	0.420		
Perforation, yes	20.366 (0.000–6.956×10^{9})	0.764		
High-grade tumor, yes	22.896 (0.087–6.050×10^{3})	0.271		
Perineural invasion, yes	1.040 (0.516–2.098)	0.913		
Lymphovascular invasion, yes	2.644 (1.284–5.448)	0.008	1.393 (0.625–3.106)	0.418
Adjuvant chemotherapy, no	3.592 (1.783–7.240)	<0.001	3.967 (1.910–8.239)	<0.001
Oxaliplatin-contained, no	2.720 (0.866–8.544)	0.087		
MMR status, low/MSS	3.804 (0.907–15.915)	0.068	2.434 (0.550–10.768)	0.241

HR, hazard ratio; CI, confidence interval; LN, lymph node; MMR, mismatch repair; MSS, microsatellite stable.

Table 3. Univariate and multivariate analyses for overall survival

Variable	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, ≥65 yr	4.629 (1.068–20.058)	0.041	2.727 (0.604–12.301)	0.192
Male sex	1.645 (0.657–4.202)	0.298	1.645 (0.598–4.525)	0.335
Primary tumor sidedness, right	1.166 (0.472–2.879)	0.739	1.301 (0.477–3.548)	0.607
Tumor stage, T4	5.324 (2.104–13.466)	<0.001	7.568 (2.313–24.766)	0.001
Sampled LNs, <12	1.076 (0.304–3.817)	0.909	1.866 (0.446–7.813)	0.393
Obstruction, yes	1.063 (0.141–8.035)	0.953		
Perforation, yes	20.336 (0.000–4.319×10^{17})	0.875		
High-grade tumor, yes	22.724 (0.011–4.899×10^{4})	0.425		
Perineural invasion, yes	2.075 (0.770–5.595)	0.149		
Lymphovascular invasion, yes	2.172 (0.831–5.675)	0.114	1.116 (0.378–3.296)	0.843
Adjuvant chemotherapy, no	3.344 (1.311–8.534)	0.012	4.525 (1.627–12.579)	0.004
Oxaliplatin-contained, no	1.957 (0.489–7.839)	0.343		
MMR status, low/MSS	0.453 (0.591–33.561)	0.147	2.812 (0.350–22.560)	0.331

HR, hazard ratio; CI, confidence interval; LN, lymph node; MMR, mismatch repair; MSS, microsatellite stable.

Nevertheless, the current findings confirm a significant survival benefit for MSI-L/MSS or pMMR intermediate-risk stage II CC patients treated with adjuvant therapy when compared to patients not receiving adjuvant therapy. Furthermore, the current analyses excluded high-risk patients with pT4 and/or <12 lymph nodes and several intermediate-risk factors known as robust risks of relapse after CC resection [4]. The current findings also narrow the indications for adjuvant chemotherapy and may help in establishing appropriate treatment strategies and disease prognosis for patients with stage II CC.

Besides clinicopathologic factors, selection of the adjuvant regimen varies depending on clinical considerations such as the patient's performance status, comorbidities and tolerance, and physician/patient preference [18]. In the current study, no survival benefits were noted when oxaliplatin was added to the adjuvant regimens for intermediate-risk stage II patients identified as MSI-L/MSS or pMMR. This result is consistent with those of previous studies. The results from a recent *post-hoc* exploratory analysis of the MOSAIC trial showed no significant DFS benefit of FOLFOX when compared with infusional 5-FU/ leucovorin [5,24]. The

NSABP-07 trial also showed no benefit from oxaliplatin-containing regimens [25]. Of note, the definition of high-risk differs among such studies, and no prospective trial has yet compared oxaliplatin-based therapy in intermediate-risk patients [20]. However, the current results clearly question the use of oxaliplatin in adjuvant chemotherapy for patients with intermediate-risk stage II CC. Therefore, further large-scale studies are required to identify the features predictive of benefit from oxaliplatin-based therapy in MSI-L/MSS or pMMR intermediate-risk stage II CC.

Interestingly, the present study demonstrated that MSI-H/dMMR status was associated with better prognosis, but this status did not predict the benefit of adjuvant chemotherapy in intermediate-risk stage II CC patients. Thus, despite substantial evidence of MSI-H/dMMR as a prognostic marker of a more favorable outcome, the role of adjuvant treatment for stage II CC patients with MSI-H/dMMR status remains unclear [11]. Several studies have also reported that MSI-H/dMMR status may be a predictive marker of decreased benefit and possibly detrimental impact of adjuvant therapy with 5-FU alone in patients with stage II CC [9,10], whereas other recent studies revealed no association with adjuvant treatment, which is consistent with the survival results of the present study [26,27]. Thus, when taken together, the current observations on the association of MSI-H/dMMR status and impact of adjuvant chemotherapy would seem to offer meaningful information and a novel strategy for patient subgroups with different risks.

The use of adjuvant chemotherapy was found to correlate with better DFS in MSI-L/MSS or pMMR intermediate-risk stage II CC patients, thereby warranting further clarification of the role of adjuvant chemotherapy and benefit of oxaliplatin-containing regimens for MSI-L/MSS or pMMR intermediate-risk stage II CC patients after curative resection.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization: BWK, JHB, JGK; Data curation: DWB, EC, HJK, SYP, JSP, GSC; Formal analysis: BWK, JHB, JGK; Visualization: BWK; Writing-original draft: BWK, JHB, JGK; Writing-review & editing: BWK, JHB, JGK.

ORCID

Byung Woog Kang, https://orcid.org/0000-0001-6357-8748
Dong Won Baek, https://orcid.org/0000-0003-4446-1549
Eunhye Chang, https://orcid.org/0000-0001-7593-5917
Hye Jin Kim, https://orcid.org/0000-0002-3370-5985
Su Yeon Park, https://orcid.org/0000-0003-4821-2101
Jun Seok Park, https://orcid.org/0000-0001-5443-6748
Gyu Seog Choi, https://orcid.org/0000-0001-5476-4610
Jin Ho Baek, https://orcid.org/0000-0003-2523-9950
Jong Gwang Kim, https://orcid.org/0000-0002-7615-5864

References

1. Des Guetz G, Uzzan B, Morere JF, Perret G, Nicolas P. Duration of adjuvant chemotherapy for patients with non-metastatic colorectal cancer. Cochrane Database Syst Rev 2010;(1):CD 007046.
2. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350: 2343–51.
3. Benson AB 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408–19.
4. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000;124:979–94.
5. André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC Study. J Clin Oncol 2015; 33:4176–87.
6. Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, et al. Colon cancer, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:329–59.
7. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993;260:816–9.
8. Markowitz SD, Bertagnolli MM. Molecular origins of cancer: molecular basis of colorectal cancer. N Engl J Med 2009;361: 2449–60.
9. Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant thera-

py in colon cancer. J Clin Oncol 2010;28:3219–26.
10. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003;349:247–57.
11. Klingbiel D, Saridaki Z, Roth AD, Bosman FT, Delorenzi M, Tejpar S. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. Ann Oncol 2015;26:126–32.
12. Argilés G, Tabernero J, Labianca R, Hochhauser D, Salazar R, Iveson T, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1291–305.
13. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
14. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696–704.
15. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011;29:1465–71.
16. Haller DG, Catalano PJ, Macdonald JS, O'Rourke MA, Frontiera MS, Jackson DV, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 2005;23:8671–8.
17. André T, Sargent D, Tabernero J, O'Connell M, Buyse M, Sobrero A, et al. Current issues in adjuvant treatment of stage II colon cancer. Ann Surg Oncol 2006;13:887–98.
18. de Gramont A, de Gramont A, Chibaudel B, Larsen AK, Tournigand C, André T, et al. The evolution of adjuvant therapy in the treatment of early-stage colon cancer. Clin Colorectal Cancer 2011;10:218–26.
19. Lindor NM, Burgart LJ, Leontovich O, Goldberg RM, Cunningham JM, Sargent DJ, et al. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. J Clin Oncol 2002;20:1043–8.
20. Chakrabarti S, Peterson CY, Sriram D, Mahipal A. Early stage colon cancer: current treatment standards, evolving paradigms, and future directions. World J Gastrointest Oncol 2020;12:808–32.
21. Dienstmann R, Salazar R, Tabernero J. Personalizing colon cancer adjuvant therapy: selecting optimal treatments for individual patients. J Clin Oncol 2015;33:1787–96.
22. Varghese A. Chemotherapy for stage II colon cancer. Clin Colon Rectal Surg 2015;28:256–61.
23. Rebuzzi SE, Pesola G, Martelli V, Sobrero AF. Adjuvant chemotherapy for stage II colon cancer. Cancers (Basel) 2020;12:2584.
24. Tournigand C, André T, Bonnetain F, Chibaudel B, Lledo G, Hickish T, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol 2012;30:3353–60.
25. Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011;29:3768–74.
26. Bertagnolli MM, Redston M, Compton CC, Niedzwiecki D, Mayer RJ, Goldberg RM, et al. Microsatellite instability and loss of heterozygosity at chromosomal location 18q: prospective evaluation of biomarkers for stages II and III colon cancer: a study of CALGB 9581 and 89803. J Clin Oncol 2011;29:3153–62.
27. Hutchins G, Southward K, Handley K, Magill L, Beaumont C, Stahlschmidt J, et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. J Clin Oncol 2011;29:1261–70.

Case report

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):150-152
https://doi.org/10.12701/yujm.2021.01060

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Twin anemia polycythemia sequence in a dichorionic diamniotic pregnancy: a case report

Soo-Young Lee[1], Jin Young Bae[2], Seong Yeon Hong[2]

[1]Department of Obstetrics and Gynecology, Yeungnam University Hospital, Daegu, Korea
[2]Department of Obstetrics and Gynecology, Daegu Catholic University School of Medicine, Daegu, Korea

Complications related to the vascular anastomosis of the placental vessels in monochorionic twins are fatal. The clinical syndromes of feto-fetal transfusion include twin anemia polycythemia sequence (TAPS), twin-twin transfusion syndrome, and twin reversed arterial perfusion sequence. We present an extremely rare case of TAPS in a dichorionic diamniotic pregnancy. A 36-year-old woman, gravida 0, para 0, was referred to our hospital with suspected preterm premature membrane rupture. Although her pelvic examination did not reveal specific findings, the non-stress test result showed minimal variability in the first fetus and late deceleration in the second one. An emergency cesarean section was performed. The placenta was fused, and one portion of the placenta was pale, while the other portion was dark red. The hemoglobin level of the first fetus was 7.8 g/dL and that of the second one was 22.2 g/dL.

Keywords: Dichorionic diamniotic twins; Fetofetal transfusion; Twin anemia polycythemia sequence; Twin to twin transfusion syndrome

Introduction

In monochorionic twins, complications may occur because of vascular anastomosis, as the placenta is shared. An imbalanced blood supply due to vascular anastomosis can lead to feto-fetal transfusion, increasing fetal morbidity. Clinical syndromes related to vascular anastomosis include twin anemia polycythemia sequence (TAPS), twin-twin transfusion syndrome (TTTS), and twin reversed arterial perfusion sequence. TTTS is a chronic form of feto-fetal transfusion that affects approximately 9% of all monochorionic twins [1]. It occurs due to unidirectional flow through the arteriovenous anastomosis, creating an imbalance of blood volume between the donor and recipient twins. The donor twin is growth restricted and develops anemia, and the recipient twin becomes polycythemic and develops heart failure, resulting in fetal hydrops. TAPS is diagnosed antenatally based on the middle cerebral artery-peak systolic velocity (MCA-PSV) when there is no amniotic fluid discordance. The term TAPS was first defined by Lopriore et al. [2] in 2007. It may occur spontaneously in up to 5% of all monochorionic twins as a result of incomplete laser treatment in TTTS cases [3]. We present a rare case of TAPS in a dichorionic pregnancy, of which only two cases have been reported so far.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2021-04-042) and written informed consent from the patient was waived by IRB.

Received: March 17, 2021 • **Revised:** May 25, 2021 • **Accepted:** June 4, 2021
Corresponding author: Seong Yeon Hong, MD, PhD
Department of Obstetrics and Gynecology, Daegu Catholic University School of Medicine, 33 Duryugongwon-ro 17-gil, Nam-gu, Daegu 42472, Korea
Tel: +82-53-650-4078 • Fax: +82-53-650-4078 • E-mail: magu815@cu.ac.kr

A 36-year-old woman, gravida 0, para 0, was referred by a local clinic to the obstetric department following a preterm premature rupture of membranes at 34 1/7 weeks of gestation related to a dichorionic diamniotic pregnancy. She had a history of hypothyroidism, gestational diabetes, unexplained infertility, and laparoscopic left salpingectomy due to an ectopic pregnancy. She had conceived via *in vitro* fertilization. Although her pregnancy was uneventful, she was hospitalized for a week because of preterm labor at 33 weeks of gestation. She was transferred to the hospital under the suspicion of preterm premature rupture of membranes. Pelvic examination revealed no specific findings. The nitrazine and Amnisure ROM (rupture of membrane) test (QIAZEN, Hilden, Germany) results were negative. The non-stress test (NST) revealed minimal variability in the first fetus, but the heart rate of the second one showed late deceleration. An emergency cesarean section was performed immediately. During delivery, the donor twin was a 1,940-g male infant with Apgar scores of 2 and 6 at 1 and 5 minutes, respectively, and the recipient twin was a 2,360-g female infant with Apgar scores of 4 and 7 at 1 and 5 minutes, respectively. Birth weight discordance was 17.8%. The hemoglobin (Hb) count of the male infant was 7.8 g/dL, with a hematocrit level of 25.2%, whereas the female infant had a Hb count of 22.2 g/dL, with a hematocrit level of 70% on day 1, fulfilling the postnatal criteria of TAPS stage 3 (inter-twin Hb difference being 14.4 g/dL). After delivery, the donor twin was transfused with 20 mL of packed red blood cells, and the recipient twin received 28 mL of exchange transfusion with normal saline after phlebotomy. The twins were discharged from the hospital after conservative treatment without brain damage or hemorrhagic shock during postnatal care. Both twins were under follow-up without any complications, but congenital nephrotic syndrome developed in the recipient twin 3 months after birth.

The placenta was macroscopically fused. One portion of the placenta was pale, while the other was dark reddish due to congestion (Fig. 1). Due to an emergency cesarean section, the vascular connection of the placenta was not confirmed.

Discussion

In 2007, Lopriore et al. [2] reported a case of severe fetal or neonatal hematological complications due to chronic inter-twin transfusion without a twin oligo-polyhydramnios sequence (TOPS) sign, which was defined as TAPS. It was diagnosed when the MCA-PSV increased to > 1.5 multiples of the median (MoM) in one fetus and decreased below 1.0 MoM in the other twin following an antenatal Doppler examination. Only 40% to 63% of TAPS cases are diagnosed antenatally [4,5]. Therefore, postnatal diagnostic criteria were proposed. These criteria are fulfilled when the difference in Hb count between the twins is > 8.0 g/dL and the reticulocyte count ratio is > 1.7, or when the placenta has only a small (diameter of < 1 mm) vascular anastomosis. Antenatal classification of TAPS categorizes this condition into five stages: stage 1, MCA-PSV > 1.5 MoM in the donor and MCA-PSV < 1.0 MoM in the recipient, without any other signs of fetal compromise; stage 2, MCA-PSV > 1.7 MoM in the donor and MCA-PSV < 0.8 MoM in the recipient, without any other signs of fetal compromise; stage 3, as stage 1 or 2, with cardiac compromise in the donor twin that is defined as a critically abnormal flow (absent or reversed end-diastolic flow in the umbilical artery, pulsatile flow in the umbilical vein, and increased pulsatility index or reversed flow in ductus venosus); stage 4, hydrops of donor twin; and stage 5, intrauterine demise of one or both fetuses preceded by TAPS [5]. The postnatal classification categorizes TAPS into five stages based on the inter-twin Hb difference as follows: stage 1, > 8.0 g/dL; stage 2, > 11.0 g/dL; stage 3, > 14.0 g/dL; stage 4, > 17.0 g/dL; and stage 5, > 20.0 g/dL [5].

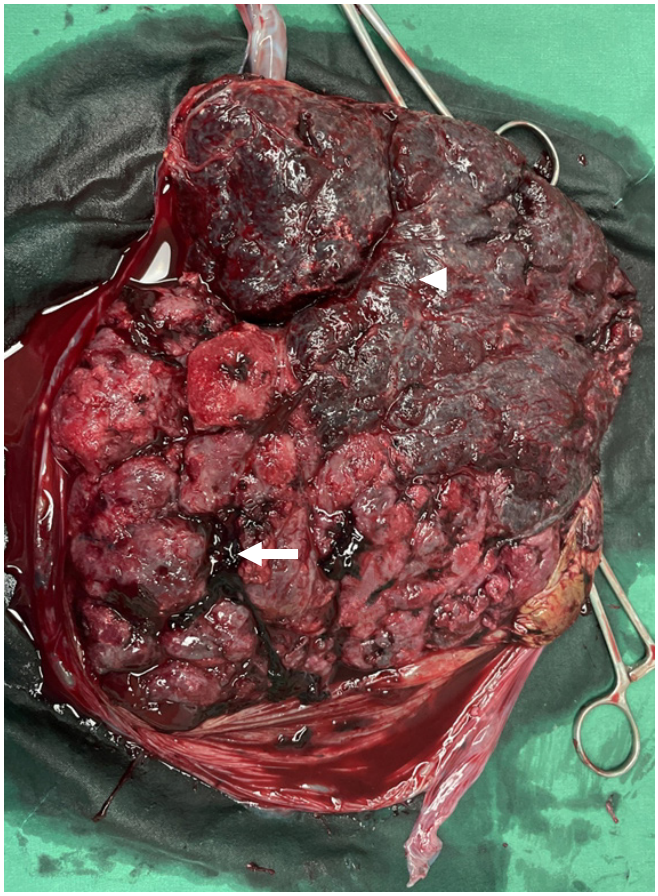

Fig. 1. Gross finding of the placenta of twin anemia polycythemia sequence in a dichorionic diamniotic pregnancy. The maternal surface shows the pale placental share of the donor twin (arrow) and the plethoric share of the recipient twin (arrowhead).

Theoretically, TAPS and TTTS do not occur in dichorionic twins; however, two cases of TAPS have been reported to date [6,7]. Besides, our study has some limitations. As emergency cesarean section was immediately decided after NST monitoring, MCA-PSV could not be measured; however, the difference in the single deepest pocket between the two fetuses was insignificant. The patient underwent antenatal care at a local clinic where complications related to pregnancy or signs of TOPS were not observed. In addition, because the genders of the two fetuses were different, TTTS and TAPS were excluded. However, such a mistake occurred because it was overlooked that TTTS and TAPS might also occur in dichorionic twins. Therefore, a biopsy was not performed to confirm placental vascular anastomosis. In this case, a differential diagnosis between TTTS and TAPS was necessary. TTTS was excluded because clinical signs of acute perinatal blood loss were observed in the donor infant whereas TOPS did not occur during antenatal care.

As described above, TAPS can only be diagnosed antenatally with MCA-PSV. According to Movva and Rijhsinghani [8], heterogeneity in placental echogenicity is helpful for the early diagnosis and management of TAPS along with timely delivery.

In conclusion, although it is very rare, if there is a TOPS sign during antenatal care in dichorionic twins or if the fetal MCA-PSV is increased in dichorionic twins, it is important to be aware that TTTS or TAPS may also occur in dichorionic twins.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization, Formal analysis, Supervision: JYB, SYH; Project administration: SYH; Writing-original draft: SYL; Writing -review & editing: SYL.

ORCID

Soo-Young Lee, https://orcid.org/0000-0001-8672-0751
Jin Young Bae, https://orcid.org/0000-0002-9287-8210
Seong Yeon Hong, https://orcid.org/0000-0001-6496-0498

References

1. Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van Mieghem T, et al. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. Am J Obstet Gynecol 2008;199:514.e1–8.
2. Lopriore E, Middeldorp JM, Oepkes D, Kanhai HH, Walther FJ, Vandenbussche FP. Twin anemia-polycythemia sequence in two monochorionic twin pairs without oligo-polyhydramnios sequence. Placenta 2007;28:47–51.
3. de Villiers SF, Slaghekke F, Middeldorp JM, Walther FJ, Oepkes D, Lopriore E. Placental characteristics in monochorionic twins with spontaneous versus post-laser twin anemia-polycythemia sequence. Placenta 2013;34:456–9.
4. Slaghekke F, Kist WJ, Oepkes D, Pasman SA, Middeldorp JM, Klumper FJ, et al. Twin anemia-polycythemia sequence: diagnostic criteria, classification, perinatal management and outcome. Fetal Diagn Ther 2010;27:181–90.
5. Tollenaar LS, Slaghekke F, Middeldorp JM, Klumper FJ, Haak MC, Oepkes D, et al. Twin anemia polycythemia sequence: current views on pathogenesis, diagnostic criteria, perinatal management, and outcome. Twin Res Hum Genet 2016;19:222–33.
6. Zilliox M, Koch A, Favre R, Sananes N. Unusual twin anemia-polycythemia sequence in a dichorionic diamniotic pregnancy. J Gynecol Obstet Hum Reprod 2019;48:359–61.
7. Tollenaar LS, Prins SA, Beuger S, Slaghekke F, Oepkes D, Lopriore E. Twin anemia polycythemia sequence in a dichorionic twin pregnancy leading to severe cerebral injury in the recipient. Fetal Diagn Ther 2021;48:321–6.
8. Movva VC, Rijhsinghani A. Discrepancy in placental echogenicity: a sign of twin anemia polycythemia sequence. Prenat Diagn 2014;34:809–11.

Case report

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):153-160
https://doi.org/10.12701/yujm.2021.01039

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Idiopathic multicentric Castleman disease presenting progressive reticular honeycomb infiltration of lung and immunoglobulin G and immunoglobulin G4 dominant hypergammaglobulinemia: a case report

Hyun-Je Kim[1], Young-Hoon Hong[2]

[1]Division of Rheumatology, Department of Internal Medicine, CHA Gumi Medical Center, CHA University, Gumi, Korea
[2]Division of Rheumatology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

Multicentric Castleman disease (MCD) is an uncommon systemic lymphoproliferative disorder that may cause multiple organ damage. Castleman disease-associated diffuse parenchymal lung disease (DPLD) has not been well studied. A 32-year-old man was referred to our hospital for progressive generalized weakness, light-headedness, and dyspnea on exertion for more than one year. Laboratory evaluations showed profound anemia, an elevated erythrocyte sedimentation rate, and an increased C-reactive protein level with polyclonal hypergammaglobulinemia. Chest radiography, computed tomography (CT), and positron emission tomography-CT scan demonstrated diffuse lung infiltration with multiple cystic lesions and multiple lymphadenopathy. In addition to these clinical laboratory findings, bone marrow, lung, and lymph node biopsies confirmed the diagnosis of idiopathic MCD (iMCD). Siltuximab, an interleukin-6 inhibitor, and glucocorticoid therapy were initiated. The patient has been tolerating the treatment well and had no disease progression or any complications in 4 years. Herein, we report this case of human herpesvirus-8-negative iMCD-associated DPLD accompanied by multiple cystic lesions, multiple lymphadenopathy, and polyclonal hypergammaglobulinemia with elevated immunoglobulin G (IgG) and IgG4 levels. We recommend a close evaluation of MCD in cases of DPLD with hypergammaglobulinemia.

Keywords: Immunoglobulin G4-related disease; Interstitial lung diseases; Langerhans-cell histiocytosis; Multicentric Castleman disease

Introduction

Castleman disease (CD) is an uncommon lymphoproliferative disorder first described by Benjamin Castleman in 1956 [1]. Clinically, CD has three distinctive subtypes; unicentric CD (UCD), human herpesvirus-8 (HHV-8)-associated multicentric CD (MCD), and idiopathic MCD (iMCD) [2]. MCD is characterized by generalized weakness, anemia, generalized lymphadenopathy, polyclonal hypergammaglobulinemia, high erythrocyte sedimentation rate (ESR), and increased C-reactive protein (CRP) levels as a consequence of elevated interleukin-6 (IL-6) levels [3]. Immunoglobulin G4-related disease (IgG4-RD) typically manifests as tumor-like enlargement of exocrine glands or extranodal tissues with an elevated serum IgG4 level. IgG4-RD occasionally involves lymph nodes. It may mimic MCD histologically [4]. Langerhans cell histiocytosis (LCH) is related to the aberrant proliferation of

Received: April 5, 2021 • **Revised:** May 21, 2021 • **Accepted:** May 25, 2021
Corresponding author: Young-Hoon Hong, MD, PhD
Division of Rheumatology, Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3841 • Fax: +82-53-654-8386 • E-mail: yhhong@med.yu.ac.kr

the mononuclear phagocyte system and Langerhans cell infiltration. Diffuse parenchymal lung disease (DPLD) with multiple cystic lesions is a characteristic finding of pulmonary LCH. Although MCD is rarely associated with DPLD, it can be considered in patients presenting with systemic inflammatory manifestations [5]. The authors encountered a case of iMCD presenting as DPLD with multiple cystic lesions accompanied by multiple lymphadenopathy and polyclonal hypergammaglobulinemia with elevated IgG and IgG4 levels. Thus, there is a need to differentiate MCD from IgG4-RD, LCH, and other DPLDs.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of CHA Gumi Medical Center, CHA University (IRB No: GM 21-07), and written informed consent from the patient was waived by the IRB.

A 32-year-old previously healthy man was referred to our hospital because of anemia and elevated ESR and CRP levels without any subjective symptoms. Without any laboratory abnormalities except for high ESR/CRP levels and anemia, upper and lower endoscopies and bone marrow studies were conducted. There were no abnormal findings. During an observational follow-up of symptomatic changes, the patient presented with insidious and progressive generalized weakness, light-headedness, and dyspnea on exertion (DOE) for more than 1 year. Routine medical examination at a local medical center revealed newly developed multiple reticular infiltrations and cystic lesions in both lung fields, as well as anemia and high levels of ESR/CRP. The patient was transferred to our hospital for further evaluation of DPLD. On admission, the patient appeared chronically ill and slightly lethargic and complained of generalized weakness and loss of appetite without a specific past medical history other than chronic anemia.

His blood pressure was 120/80 mmHg, heart rate was 92 beats/min, respiratory rate was 20 breaths/min, and body temperature was 37.3°C. Initial laboratory tests revealed a white blood cell (WBC) count of 6,770/μL, hemoglobin (Hb) of 6.5 g/dL, platelet count of 584,000/μL, ESR of 40 mm/hr, CRP of 16.5 mg/dL, serum total protein (TP) of 12.09 g/dL, serum albumin (Alb) of 1.79 g/dL, Alb/globulin (A/G ratio) of 0.2, IgG8 of 190 mg/dL (range, 700–1,600 mg/dL), IgG4 subclass of 2,098 mg/L (range, 39.2–864 mg/L), IL-6 of 117.1 pg/mL (≤ 8 pg/mL), and HHV-8 polymerase chain reaction negative. Protein electrophoresis results showed polyclonal gammopathy without monoclonal paraproteinemia, consistent with IgG-predominant hypergammaglobulinemia and anemia of chronic inflammation. Chest X-rays showed dense infiltrations in both lung fields (Fig. 1A–1C). Chest computed tomography (CT) scan revealed multifocal ground-glass opacity with the progression of multiple variable-sized cystic lesions as compared with that of a local medical center. There were multiple enlarged lymph nodes in the neck (I to V levels), axillae, upper and lower paratracheal, hilar, subaortic, and subcarinal areas (Fig. 1D-1H). These lesions were radiologically diagnosed as pulmonary LCH. The patient underwent positron emission tomography-CT (PET-CT) for the evaluation of lymphoproliferative diseases, lymphoma, and other malignancies. The ^{18}F-fluorodeoxyglucose uptake was diffusely enhanced in both lung parenchyma, bone marrow of the pelvis to femurs, and multilevel lymph nodes throughout the body on a PET-CT scan (Fig. 2). To evaluate polyclonal hypergammaglobulinemia and anemia, bone marrow aspiration and biopsy were performed. Bone marrow studies revealed that hypercellular marrow particles (80% cellularity), myeloid, and erythroid cells were normally mature and megakaryocytes were mildly increased in number. However, plasma cells were markedly proliferated up to 11% based on the absolute neutrophil count (Fig. 3).

An excisional biopsy was performed targeting the left external inguinal lymph nodes. The biopsy showed marked interfollicular plasmacytosis and regressed germinal centers (Fig. 4A, 4B) with IgG4 positivity of more than 100/high power field (HPF) and 70% on immunohistochemical staining (Fig. 4C, 4D). Finally, the patient underwent video-assisted thoracic surgery with wedge lung resections of the right middle and lower lobes. Histopathological findings showed dense plasmacytic and histiocytic infiltrations in the interstitium with multifocal lymphoid aggregates (Fig. 5). However, there was no evidence for the presence of Langerhans cells, eosinophils, neutrophil-forming giant cells, or abscesses. Immunohistochemical staining revealed that IgG and IgG4 positive cells were more than 400/HPF and 100/HPF, respectively. They were negative for HHV-8 and S-100 proteins.

In addition to the above examinations, the patient tested negative for HHV-8, Epstein-Barr virus, cytomegalovirus, and toxoplasmosis. He was negative for autoimmune/autoinflammatory disorders such as systemic lupus erythematosus, rheumatoid arthritis, and adult-onset still disease. The laboratory results showed fluorescent anti-nuclear antibody titer of 1:40, dsDNA IgG of 13 IU/mL (< 15 IU/mL), anti-ribonuclear protein antibody (Ab) of 0.53 U/mL (< 10 U/mL), and anti-Smith Ab of 0.3 U/mL (< 10 U/mL). The patient was also negative for polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. Based on germinal center regression and plasmacytosis with histopathologic features of enlarged lymph nodes at

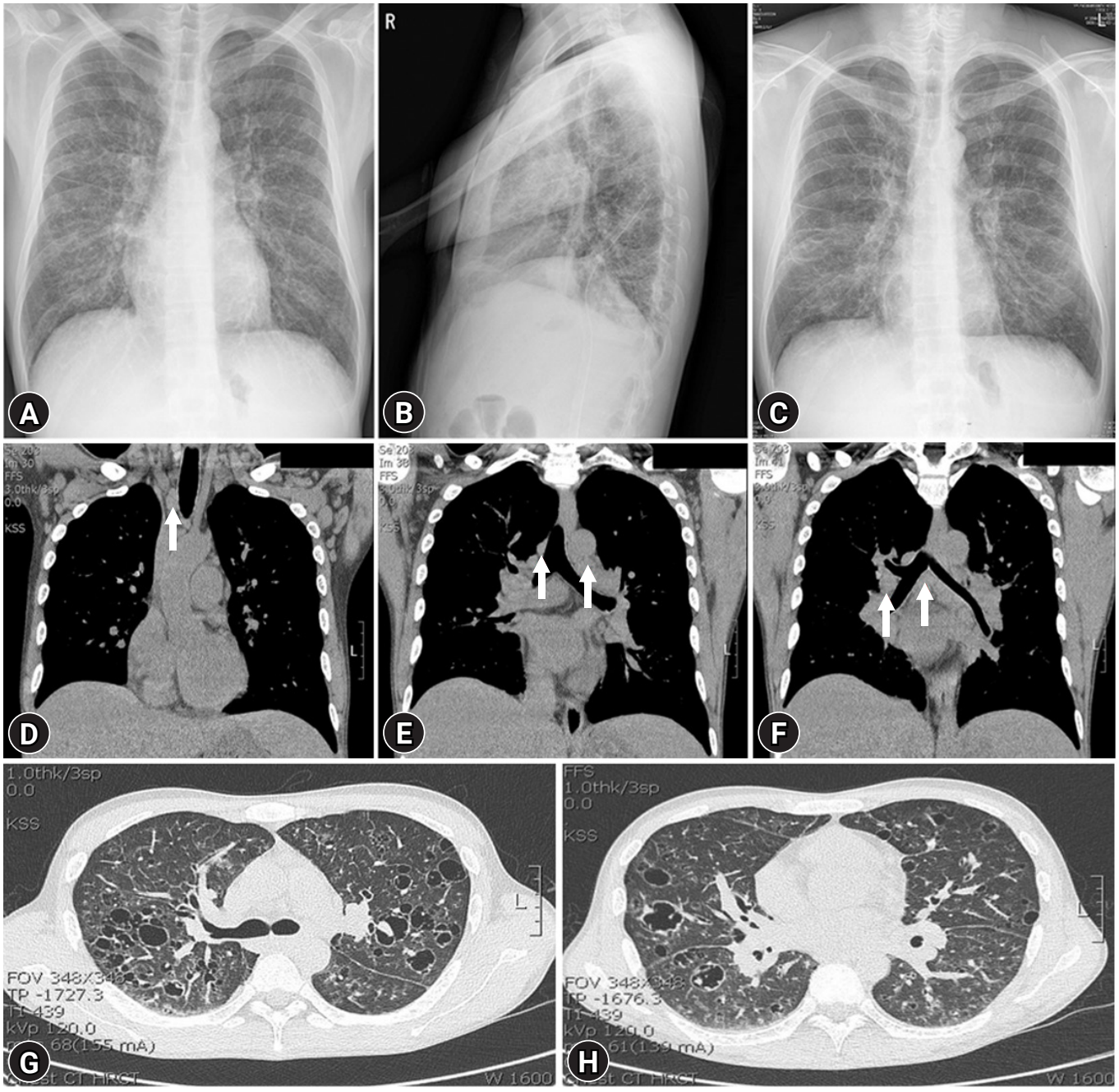

Fig. 1. (A–C) Fibrostreaky opacity and dense infiltrations are seen on both lower lung fields in initial chest X-rays (A, B) and a follow-up chest anteroposterior X-ray (C). (D, E) Coronal chest computed tomography (CT) images reveal multiple enlarged lymph nodes in both upper (D) and lower paratracheal, subaortic (E), hilar, and subcarinal areas (F) (arrows). (G, H) Axial chest CT images show multifocal ground-glass opacity with multiple variable-sized cystic lesions in both lower lung fields.

≥2 different sites, elevated ESR/CRP, anemia, thrombocytosis, hypoalbuminemia, and polyclonal hypergammaglobulinemia on laboratory tests accompanied by constitutional symptoms, hepatosplenomegaly, and lymphocytic interstitial pneumonitis, plasma cell histopathologic subtype of HHV-8-negative iMCD-complicated DPLD was diagnosed in accordance with the International, evidence-based consensus diagnostic criteria for HHV-8-negative/iMCD [6] and the 2019 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) Classification criteria for IgG4-RD [7]. High-dose prednisolone therapy (60 mg/day) was initiated. With high-dose glucocorticoid monotherapy, symptoms of generalized weakness and DOE showed improvement. However, responses were partial and limited in a dose-dependent manner after 4 weeks of treatment. Con-

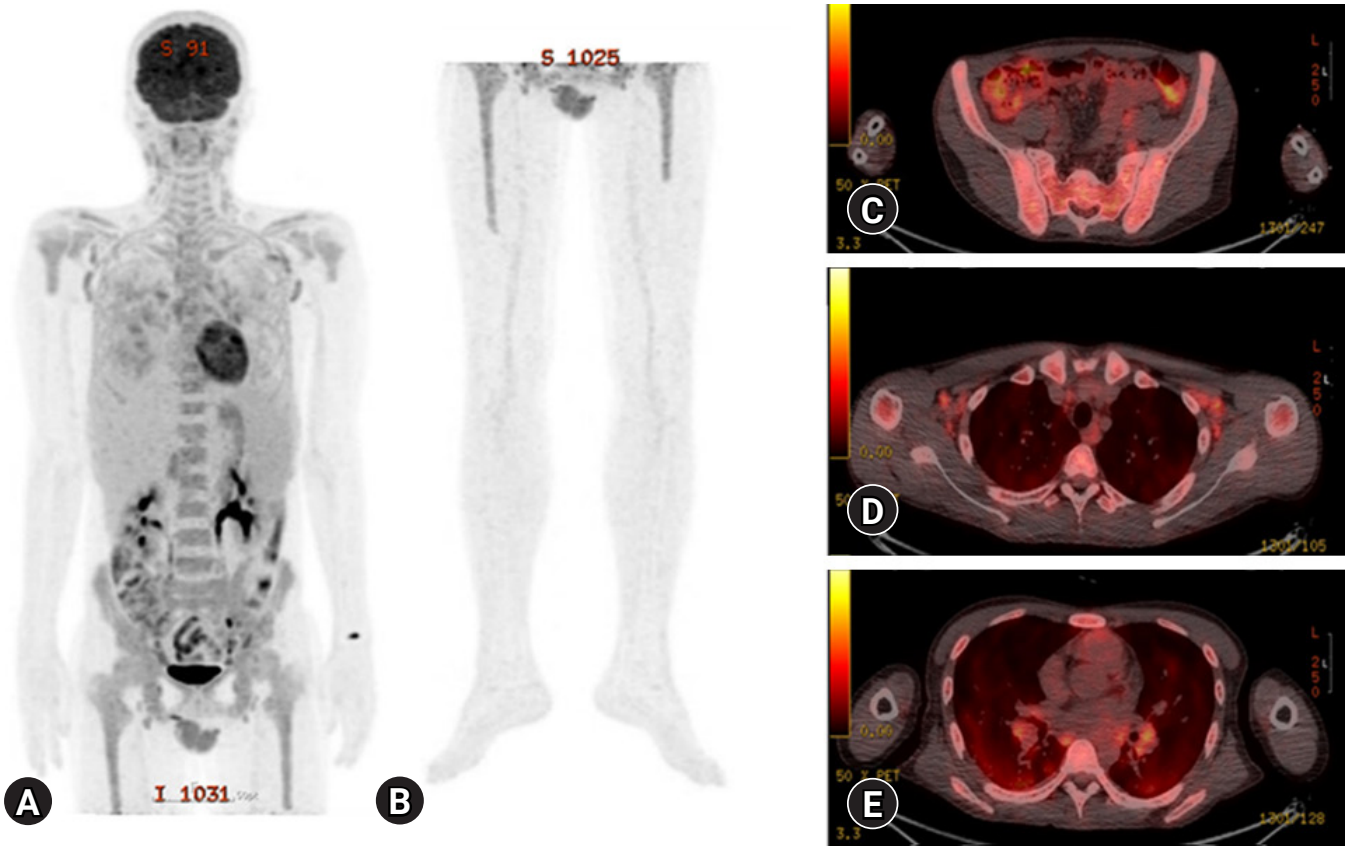

Fig. 2. (A-C) Diffusely enhanced ^{18}F-fluorodeoxyglucose uptake is seen in the bone marrow of shoulders, pelvis to femurs, (D) both axillary and both paratracheal lymph nodes, (E) and lung parenchyma with multiple cystic lesions and both prevascular lymph nodes on a positron emission tomography-computed tomography scan.

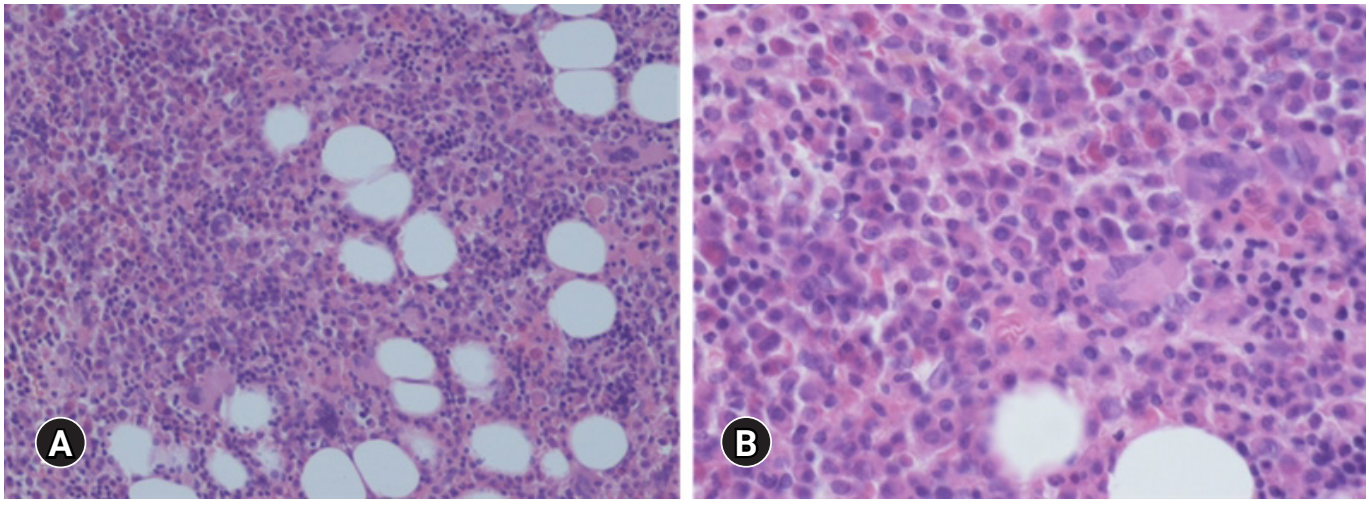

Fig. 3. (A) Bone marrow needle biopsy reveals hypercellular marrow with plasmacytosis. Plasma cells were increased up to 11.0% of absolute neutrophil count. (B) Binucleated plasma cells are occasionally seen (hematoxylin and eosin stain, [A] x100, [B] x200).

trary to the improvement in symptoms, no radiological improvement was observed on chest radiography. Responses based on follow-up laboratory tests were very subtle, showing a WBC count of 14,080/μL, Hb of 10 g/dL, platelet count of 695,000/μL, ESR of 120 mm/hr, CRP of 16.9 mg/dL, TP of 10.9 g/dL, Alb of 1.97, A/G ratio of 0.2, IgG of 6,698 mg/dL, and IgG4 sub-

 https://doi.org/10.12701/yujm.2021.01039

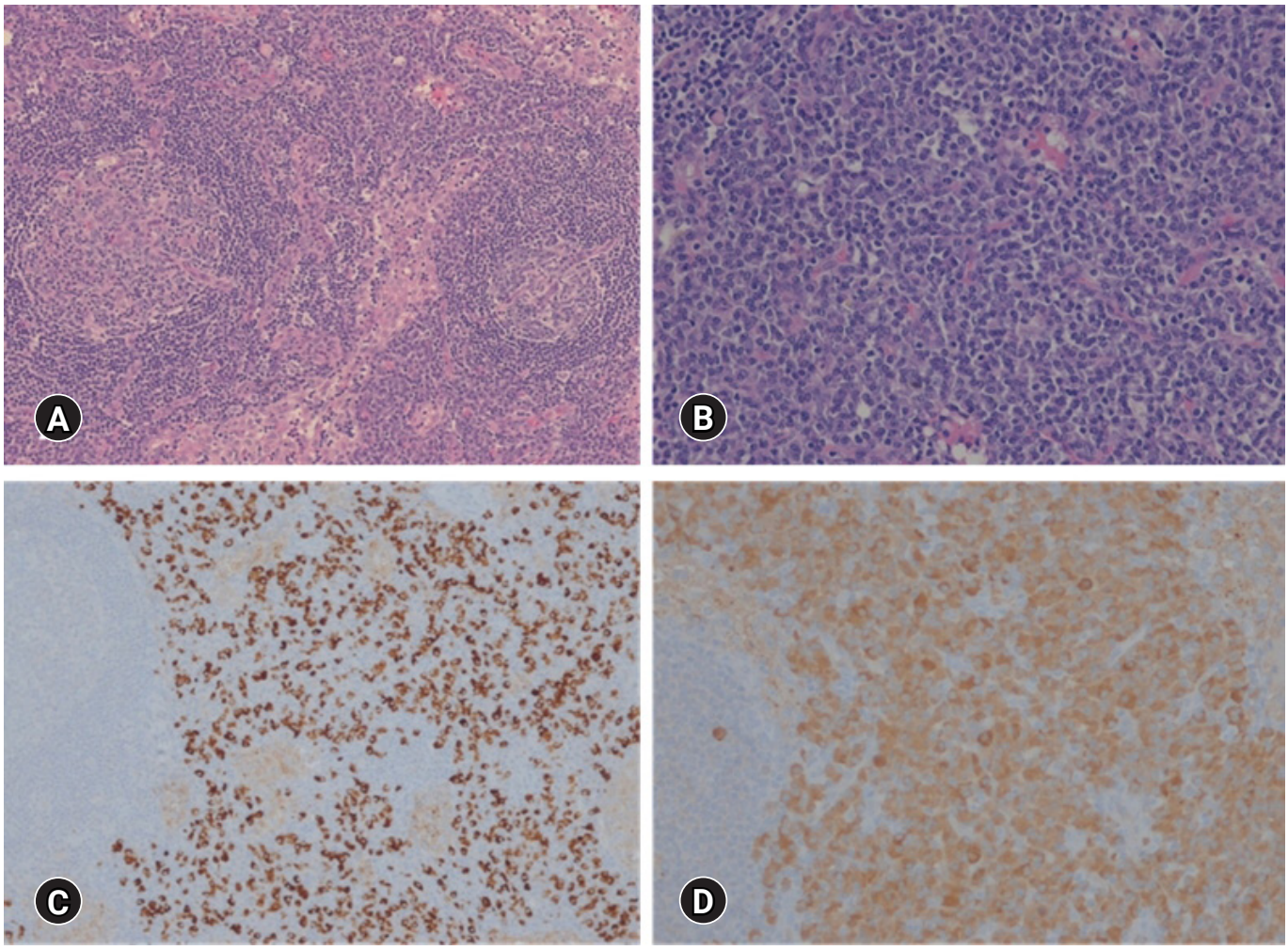

Fig. 4. (A) An inguinal lymph node shows a marked interfollicular plasmacytosis. (B) Interfollicular zones are densely populated by mature plasma cells (hematoxylin and eosin stain, [A] x100, [B] x200). (C, D) Immunohistochemical staining for immunoglobulin G (IgG) demonstrating IgG-positive cells at more than 100/high power field (C) and IgG4-positive cells (D). The ratio of IgG4-positive to IgG-positive cells is about 70% (immunohistochemical stain, [C] x100, [D] x200).

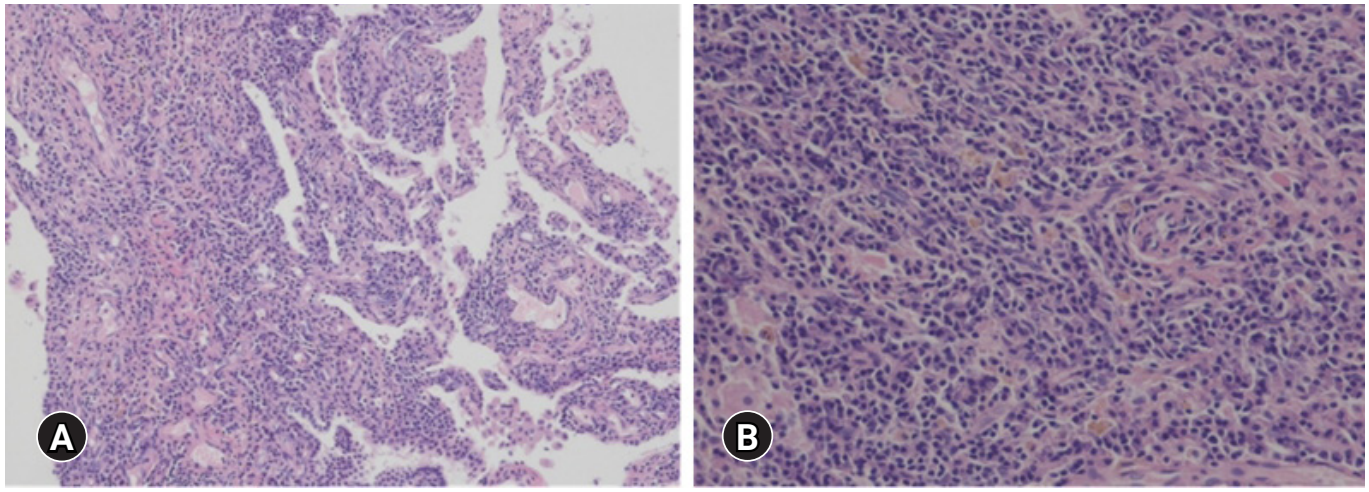

Fig. 5. (A) Wedge resection of right lower lung shows dense plasmacytic and histiocytic infiltration in the interstitium with multifocal lymphoid aggregates. (B) The infiltration of confluent plasma cells into the interstitial tissue of the lung is present (hematoxylin and eosin stain, [A] x100, [B] x200).

class of 1,523 mg/dL.

Without any significant improvement on glucocorticoid monotherapy, an IL-6 inhibitor, siltuximab (11 mg/kg, every 3 weeks), was administered while tapering prednisolone. On continuing siltuximab administration with low dose prednisolone (5 mg/day), laboratory tests resulted in Hb of 12.2 g/dL, CRP of 10.1 mg/dL, TP of 9.9 g/dL, Alb of 3.08 g/dL, and A/G ratio of 0.5. Although multiple variable-sized cystic lesions in both lungs were observed persistently, ill-defined patchy and nodular ground-glass attenuations and small well-defined nodules were decreased in both extent and size. On a follow-up chest CT, regression of enlarged lymph nodes was observed in bilateral neck, axillae, and mediastinum. After treatment for more than 30 months, the patient has maintained a favorable partial response to siltuximab without further progression or complications.

Discussion

CD is a lymphoproliferative disorder characterized by generalized lymphadenopathy and systemic inflammatory manifestations. CD can be diagnosed by excluding CD-like lesions in the context of other diseases such as lymphoma, POEMS syndrome, primary lymph node plasmacytoma, follicular dendritic sarcoma, systemic lupus erythematosus, Sjögren syndrome, and IgG4-RD. Three distinct histological types are considered at diagnosis according to the features of the affected lymph nodes; hyaline-vascular type, plasma cell type, and mixed type [6,8]. Clinically, UCD is a localized disease. It usually exhibits hyaline vascular morphological changes with an excellent prognosis, whereas MCD is a systemic disease with polyclonal plasmacytic proliferation, probably due to an immunoregulatory deficit involving inflammatory signs such as lymphadenopathy, fever, splenomegaly, edema, weight loss, polyclonal lymphoproliferation, and life-threatening multiple organ dysfunction [6,9] due to IL-6 overproduction from activated plasma cells [10]. MCD is most commonly associated with HHV-8 or HIV. HHV-8 or the HIV-free state can be designated as iMCD.

CD-associated DPLDs are rare and have not been well reported [5]. However, one study based on chest CT scans has suggested that CD-associated DPLD might be more prevalent and that a well-designed prospective study should be performed [5].

In the present case, the patient visited the hospital several years ago for the evaluation of anemia and elevated ESR and CRP levels without subjective symptoms. However, during the observation period, generalized weakness and DOE developed over a 1-year period. No other infections, autoimmune/autoinflammatory disorders, hematologic diseases, or malignancies were found except for profound anemia, polyclonal hypergammaglobulinemia, and high ESR/CRP levels. A chest CT scan revealed ground-glass opacity with multiple cystic lesions consistent with LCH.

Cystic lesions in both lungs and radiologic findings were consistent with pulmonary LCH. LCH is characterized by aberrant function and proliferation of cells of the mononuclear phagocyte system and infiltration of organs by Langerhans cells [11]. Typical pathologic findings of LCH are heterogeneous collections of Langerhans cells with eosinophils, neutrophils, small lymphocytes, and histiocytes that might form multinucleated giant cells. Occasionally, eosinophilic abscesses might be present, demonstrating central necrosis and positive S-100 protein, CD1a, and HLA-DR in immunohistochemical stains [11]. However, in the present case, lung biopsy showed no presence of Langerhans cells and negative staining for S-100 protein. Bone marrow aspiration and biopsy revealed hypercellular marrow (cellularity of 80%) with an increase in plasma cells (11.0%). There was no evidence of Langerhans cell disease on lymph node biopsy.

An excisional biopsy of the lymph node showed interfollicular marked plasmacytosis, regressed germinal centers with IgG4 positivity of more than 70%, and 100/HPF on immunohistochemical staining. Wedge resections of the lung histologically demonstrated dense plasmacytic and histiocytic infiltration in the interstitium with multifocal lymphoid aggregates and negative immunohistochemical staining of HHV8 and S-100 protein. However, IgG and IgG4 positive cells were as many as 400/HPF and 100/HPF, respectively.

IgG4-RD is pathologically characterized by diffuse lymphoplasmacytic infiltration, occasional eosinophilic infiltration, irregular fibrosis, and obliterative phlebitis with infiltration of IgG4-positive plasma cells into affected tissues, including the lungs [12]. Based on radiological, histological, and clinical features, the patient was evaluated for differential diagnoses of LCH, IgG4-RD, and iMCD. In accordance with the International, evidence-based consensus diagnostic criteria for HHV-8-negative/iMCD [6] and the 2019 ACR and EULAR Classification Criteria for IgG4-RD [7], clinical and laboratory findings were taken into consideration in association with histopathological features for the final diagnosis. Mochizuki et al. [13] reported overlapping features of IgG4-RD and MCD in a single patient treated with rituximab. Sato et al. [14] studied the clinical and pathological features of IgG4-related lymphadenopathy in comparison with hyper-IL-6 syndromes such as MCD, rheumatoid arthritis, and other immune-mediated conditions. Patients with hyper-IL-6 syndromes often fulfill the criteria for IgG4-RD, showing the same histological findings. As for the differential diagnosis, Sato et al. [14] have suggested that laboratory analyses are crucial and that hyper-IL-6 syndromes are characterized by high levels of serum gamma globulin and CRP,

thrombocytosis, anemia, hypoalbuminemia, hypergammaglobulinemia, and hypocholesterolemia, which is not true for IgG4-RD. Our patient's serum levels of IL-6, immunoglobulins, and CRP were consistently high along with thrombocytosis and anemia, suggesting MCD clinically.

Based on histopathological and laboratory results along with clinical features, the patient was diagnosed with a plasma cell histopathologic subtype of HHV-8-negative iMCD-complicated DPLD. Medical therapy for MCD includes the use of glucocorticoids, monoclonal antibodies (mAb) against IL-6, chemotherapy, immune-modulators/suppressants such as thalidomide, immunoglobulin, rituximab, and hematopoietic cell transplantation [15]. With high-dose prednisolone, patient's weakness, DOE, laboratory findings of anemia, high levels of ESR/CRP, and hypergammaglobulinemia started to improve. However, the effects were partial, dose-dependent, and limited, without radiological pulmonary improvements. Glucocorticoids are frequently used as systemic therapy for patients with iMCD. They can lead to mild symptomatic improvement during acute exacerbations of iMCD. However, glucocorticoid monotherapy was found to have no significant effect on the disease. Disease relapse was observed during tapering.

According to the International, evidence-based consensus treatment guidelines for iMCD [16], siltuximab is recommended as initial therapy for patients with non-severe HHV-8 negative iMCD. Tocilizumab can be used if siltuximab is not available. Patients who do not respond to siltuximab or tocilizumab should be considered for rituximab-based therapy in combination with steroids. Patients with severe iMCD should be treated with siltuximab and high-dose steroids. If no clear response occurs within one week, combination chemotherapy should be considered. Patients with severe iMCD must have at least two of the following five criteria: (1) European Cooperative Oncology Group performance score of ≥ 2, (2) stage IV renal dysfunction (estimated glomerular filtration rate of < 30 mL/min/1.73 m^2), (3) creatinine of > 3.0, (4) anasarca and/or ascites and/or pleural/ pericardial effusion, and (5) Hb of ≤ 8.0 g/dL pulmonary involvement/interstitial pneumonitis with dyspnea.

The mAb targeting IL-6 (siltuximab) or the IL-6 receptor (tocilizumab, atlizumab) can be used in iMCD without POEMS syndrome. In a prospective randomized placebo-controlled trial investigating the efficacy of IL-6-neutralizing mAb siltuximab on iMCD [17], the median treatment duration for 19 patients was 5.1 years (range, 3.4–7.2 years), with 14 patients (74%) treated for more than 4 years. All iMCD patients in this extension study received siltuximab for a prolonged duration (up to 7 years) without evidence of cumulative toxicity or treatment discontinuation. They showed sustained disease control.

In the aspect of prognosis, IgG4-RD is known to be typically responsive to steroid therapy [18]. In one study with 10 cases of IgG4-related lung disease, all patients except one were effectively treated with prednisolone alone, and the remaining patient responded to cyclosporine [19]. In contrast, the prognosis of MCD is generally poor. In a review series of MCD, the 2-year survival was 88% (95% confidence interval, 81%–95%) for a total of 114 patients with a median follow-up period of 29 months [19]. The most common causes of death in MCD are organ failure, sepsis, malignancy, and disease progression [20].

In the present case, the patient tolerated combination therapy of siltuximab (11 mg/kg, every 3 weeks) and prednisolone (5 mg/day), showing no disease progression or any complication for 4 years.

We report a case of iMCD presenting with atypical lung manifestations mimicking LCH and IgG4-RD with IgG/IgG4 dominant hypergammaglobulinemia. Our results suggest that further evaluation of MCD should be considered in the case of DPLD with hypergammaglobulinemia, although with low probability.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Investigation, Resources, Software, Supervision, Validation: HJK, YHH; Writing - original draft: HJK, YHH; Writing - review & editing: HJK, YHH.

ORCID

Hyun-Je Kim, https://orcid.org/0000-0003-1075-5645
Young-Hoon Hong, https://orcid.org/0000-0001-8119-0464

References

1. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 1956;9:822–30.
2. Fajgenbaum DC, Shilling D. Castleman disease pathogenesis. Hematol Oncol Clin North Am 2018;32:11–21.
3. Shahidi H, Myers JL, Kvale PA. Castleman's disease. Mayo Clin

Proc 1995;70:969–77.
4. Takenaka K, Takada K, Kobayashi D, Moriguchi M, Harigai M, Miyasaka N. A case of IgG4-related disease with features of Mikulicz's disease, and retroperitoneal fibrosis and lymphadenopathy mimicking Castleman's disease. Mod Rheumatol 2011;21:410–4.
5. Huang H, Feng R, Li J, Song X, Li S, Xu K, et al. Castleman disease-associated diffuse parenchymal lung disease: A STROBE-compliant retrospective observational analysis of 22 cases in a tertiary Chinese hospital. Medicine (Baltimore) 2017;96:e8173.
6. Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129:1646–57.
7. Wallace ZS, Naden RP, Chari S, Choi H, Della-Torre E, Dicaire JF, et al. The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. Arthritis Rheumatol 2020;72:7–19.
8. Oksenhendler E, Boutboul D, Fajgenbaum D, Mirouse A, Fieschi C, Malphettes M, et al. The full spectrum of Castleman disease: 273 patients studied over 20 years. Br J Haematol 2018;180:206–16.
9. Bowne WB, Lewis JJ, Filippa DA, Niesvizky R, Brooks AD, Burt ME, et al. The management of unicentric and multicentric Castleman's disease: a report of 16 cases and a review of the literature. Cancer 1999;85:706–17.
10. Palestro G, Turrini F, Pagano M, Chiusa L. Castleman's disease. Adv Clin Path 1999;3:11–22.
11. Vassallo R, Ryu JH, Colby TV, Hartman T, Limper AH. Pulmonary Langerhans'-cell histiocytosis. N Engl J Med 2000;342:1969–78.
12. Inoue D, Zen Y, Abo H, Gabata T, Demachi H, Kobayashi T, et al. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. Radiology 2009;251:260–70.
13. Mochizuki H, Kato M, Higuchi T, Koyamada R, Arai S, Okada S, et al. Overlap of IgG4-related disease and multicentric Castleman's disease in a patient with skin lesions. Intern Med 2017;56:1095–9.
14. Sato Y, Kojima M, Takata K, Morito T, Asaoku H, Takeuchi T, et al. Systemic IgG4-related lymphadenopathy: a clinical and pathologic comparison to multicentric Castleman's disease. Mod Pathol 2009;22:589–99.
15. van Rhee F, Voorhees P, Dispenzieri A, Fosså A, Srkalovic G, Ide M, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018;132:2115–24.
16. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol 2003;38:982–4.
17. Yamashita K, Haga H, Kobashi Y, Miyagawa-Hayashino A, Yoshizawa A, Manabe T. Lung involvement in IgG4-related lymphoplasmacytic vasculitis and interstitial fibrosis: report of 3 cases and review of the literature. Am J Surg Pathol 2008;32:1620–6.
18. Liu AY, Nabel CS, Finkelman BS, Ruth JR, Kurzrock R, van Rhee F, et al. Idiopathic multicentric Castleman's disease: a systematic literature review. Lancet Haematol 2016;3:e163–75.
19. van Rhee F, Greenway A, Stone K. Treatment of idiopathic Castleman disease. Hematol Oncol Clin North Am 2018;32:89–106.
20. van Rhee F, Casper C, Voorhees PM, Fayad LE, van de Velde H, Vermeulen J, et al. A phase 2, open-label, multicenter study of the long-term safety of siltuximab (an anti-interleukin-6 monoclonal antibody) in patients with multicentric Castleman disease. Oncotarget 2015;6:30408–19.

Case report

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):161-167
https://doi.org/10.12701/yujm.2021.01179

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Congenital web of the common bile duct combined with multiple intrahepatic duct stricture: a case report of successful radiological intervention

Hanseul Lim[1], Shin Hwang[1], Gi-Young Ko[2], Hyejin Han[1]

[1]Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[2]Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Congenital web formations are extremely rare anomalies of the extrahepatic biliary tree. We herein report a case of common bile duct septum combined with multiple intrahepatic bile duct strictures in a 74-year-old female patient who was successfully treated with radiological intervention. The patient initially visited the hospital because of upper abdominal pain. Imaging studies revealed multifocal strictures with dilatation in both intra- and extrahepatic ducts; the final clinical diagnosis was congenital common bile duct web combined with multiple intrahepatic duct strictures. Surgical treatment was not indicated because multiple biliary strictures were untreatable, and the disease was clinically diagnosed as benign. The multiple strictures were extensively dilated twice through bilateral percutaneous transhepatic biliary drainage (PTBD) for 2 months. After 1 month of observation, PTBD catheters were successfully removed. The patient is doing well at 6 months after completion of the radiological intervention, with the maintenance of normal liver function. Congenital web of the bile duct is very rare, and its treatment may vary depending on the patterns of biliary stenosis. In cases where surgical intervention is not indicated for congenital web and its associated disease, radiological intervention with balloon dilatation can be a viable therapeutic option.

Keywords: Bile duct obstruction; Congenital anomaly; External drainage; Interventional radiology; Obstructive jaundice

Introduction

The incidence of congenital anomalies of the extrahepatic biliary system is approximately 10% [1]. The vast number of these anomalies are asymptomatic, and they may be diagnosed as incidentally identified findings during cholecystectomy or living liver donor work-up [2,3]. Congenital web formations are extremely rare anomalies of the extrahepatic biliary tree. The clinical manifestations of congenital webs or strictures of the extrahepatic ducts include obstructive jaundice, dilatation of the proximal bile ducts, or spontaneous rupture of the extrahepatic biliary system. A considerable proportion of patients with congenital webs might live without any recognizable symptoms for a long period, probably due to partial biliary obstruction. They can be diagnosed with a congenital web of the extrahepatic biliary tree in adulthood, with the exclusion of other known causes of acquired stricture or web formation. Herein, we report a case of common bile duct (CBD) septum combined with multiple intrahepatic bile duct strictures in a 74-year-old female patient who was successfully treated with radiological intervention.

Received: June 1, 2021 • **Revised:** June 12, 2021 • **Accepted:** June 12, 2021
Corresponding author: Shin Hwang, MD, PhD, FACS
Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Olympic-ro 43-gil 88, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3930 • Fax: +82-2-3010-6701 • E-mail: shwang@amc.seoul.kr

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No: 2021-0683), and informed consent was obtained from the patient.

A 74-year-old female patient was referred to our institution with a diagnosis of hilar bile duct stenosis. The patient was admitted to a local hospital because of upper abdominal pain. At that time, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, and cancer antigen 19-9 (CA 19-9) were elevated to 1,870 IU/mL, 1,390 IU/mL, 1.4 mg/dL, and 177 U/mL, respectively. Abdominal computed tomography (CT) showed diffuse dilatation of the intra- and extrahepatic bile ducts (Fig. 1A, 1B). Magnetic resonance cholangiopancreatography (MRCP) showed multifocal biliary webs without an anomalous pancreaticobiliary junction (Fig. 1C, 1D). Passage of the CBD web through endoscopic retrograde cholangiopancreatography had failed, so a left percutaneous transhepatic biliary drainage (PTBD) catheter was inserted. Brush cytology of the CBD showed mild, nonspecific chronic inflammation.

After the liver transaminase levels were normalized, the patient was admitted to our institution for further evaluation and treatment. MRCP performed at our institution showed multifocal stricture with dilatation in both intra- and extrahepatic ducts, suggesting that the stricture was more likely to be benign than malignant (Fig. 2). The serum CA 19-9 level was reduced to 22 U/mL. Fluorodeoxyglucose positron emission tomography-CT showed no significant hypermetabolic activity, suggesting a primary lesion in the hepatobiliary system, thereby suggesting that a benign CBD stricture was more likely than a low metabolic malignant stricture.

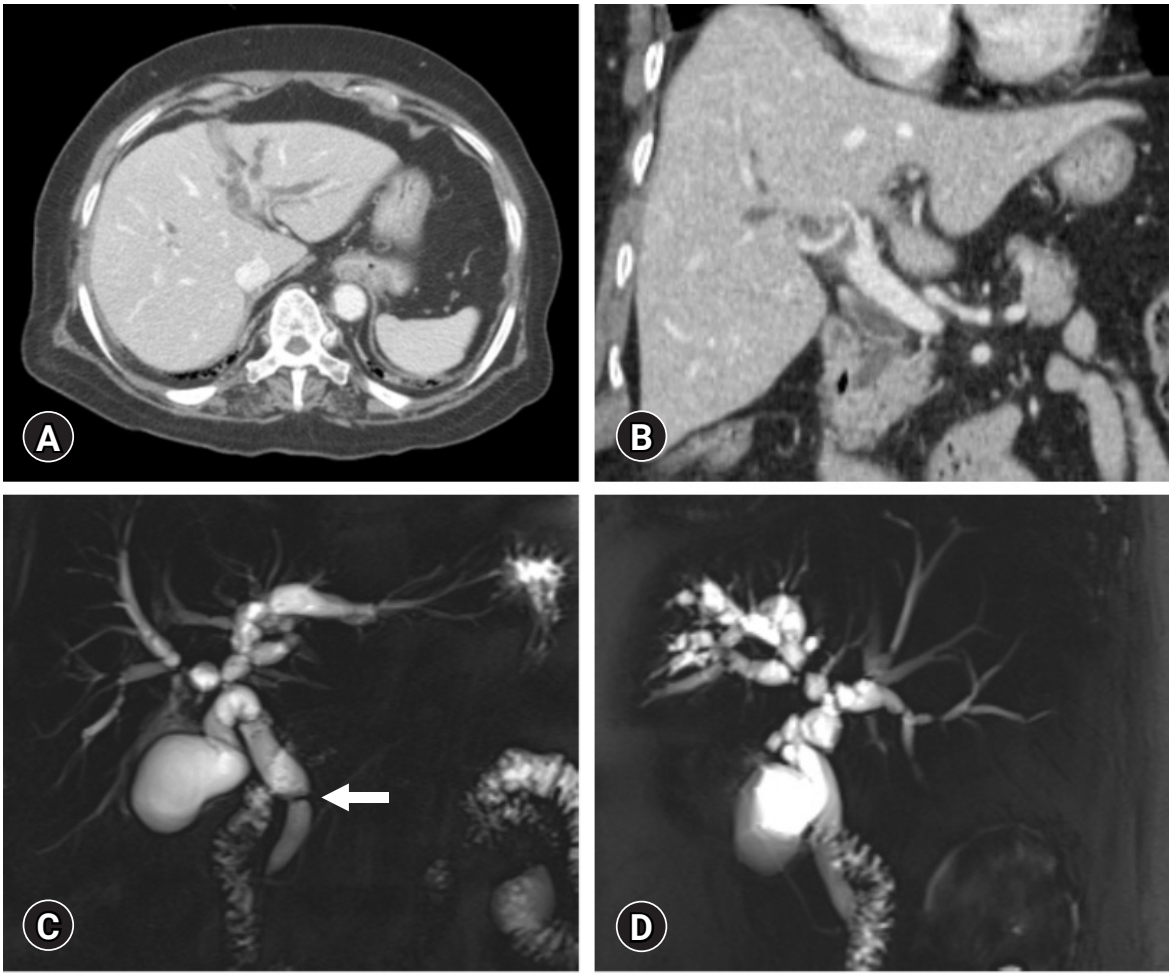

Fig. 1. Initial imaging studies. (A, B) Abdominal computed tomography shows diffuse dilatation of the intra- and extrahepatic bile ducts. (C, D) Magnetic resonance cholangiopancreatography shows multifocal biliary webs without anomalous pancreaticobiliary junction. Arrow indicates the location of a common bile duct web.

 https://doi.org/10.12701/yujm.2021.01179

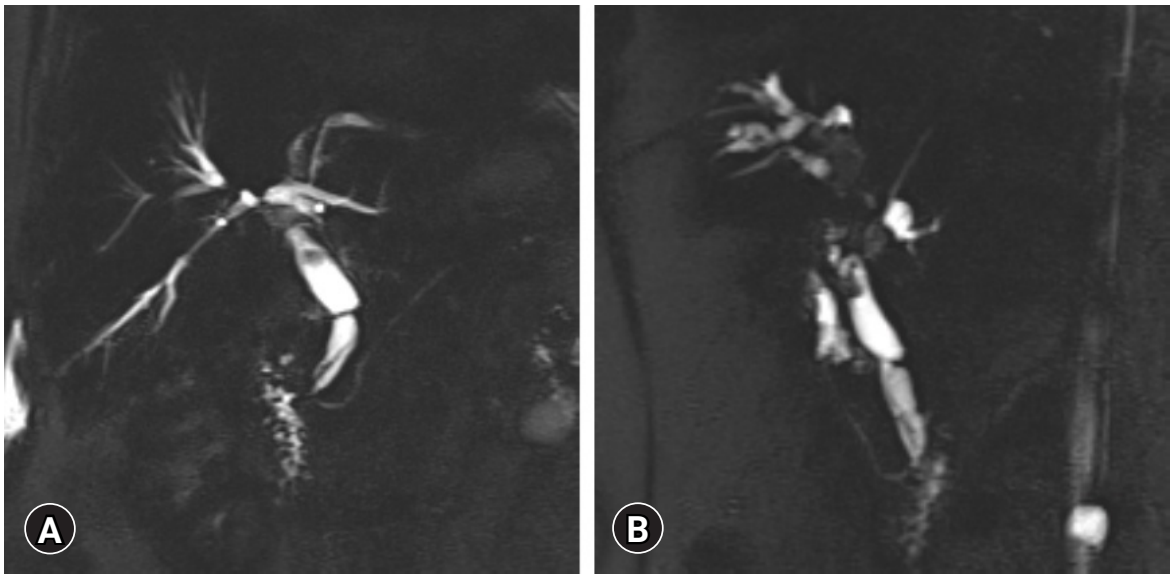

Fig. 2. The second magnetic resonance cholangiopancreatography shows multifocal stricture with dilatation in both intra- and extrahepatic ducts, suggesting that the stricture is more likely to be benign than malignant. The (A) location and (B) degree of the multifocal strictures are visualized.

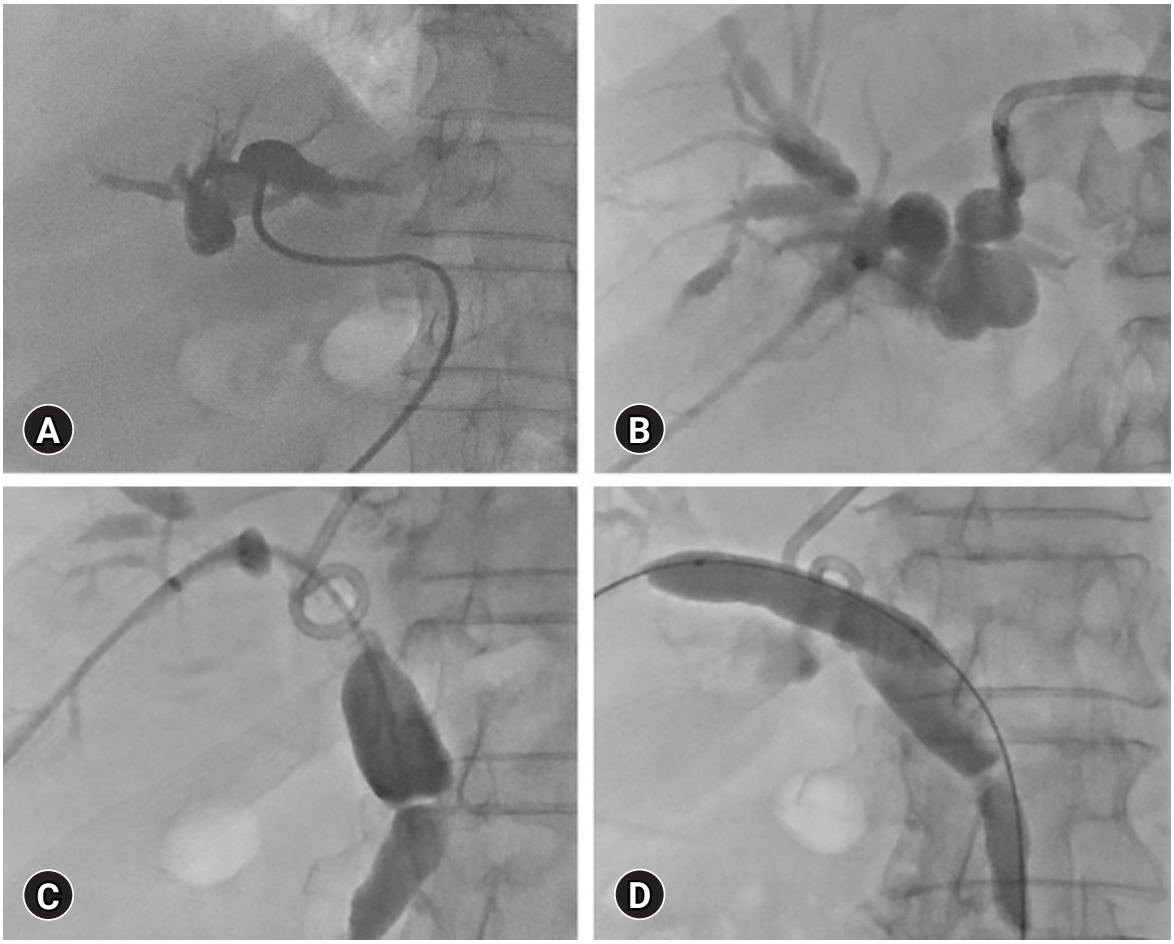

Fig. 3. Direct cholangiography findings. (A) The left-sided tubogram shows complete occlusion of the left hepatic duct. (B) The right-sided tubogram shows bile duct occlusion at the hepatic hilum. (C, D) The common bile duct web is finally cannulated after repeated trials, and then balloon dilatation of the intra- and extrahepatic stricture is performed.

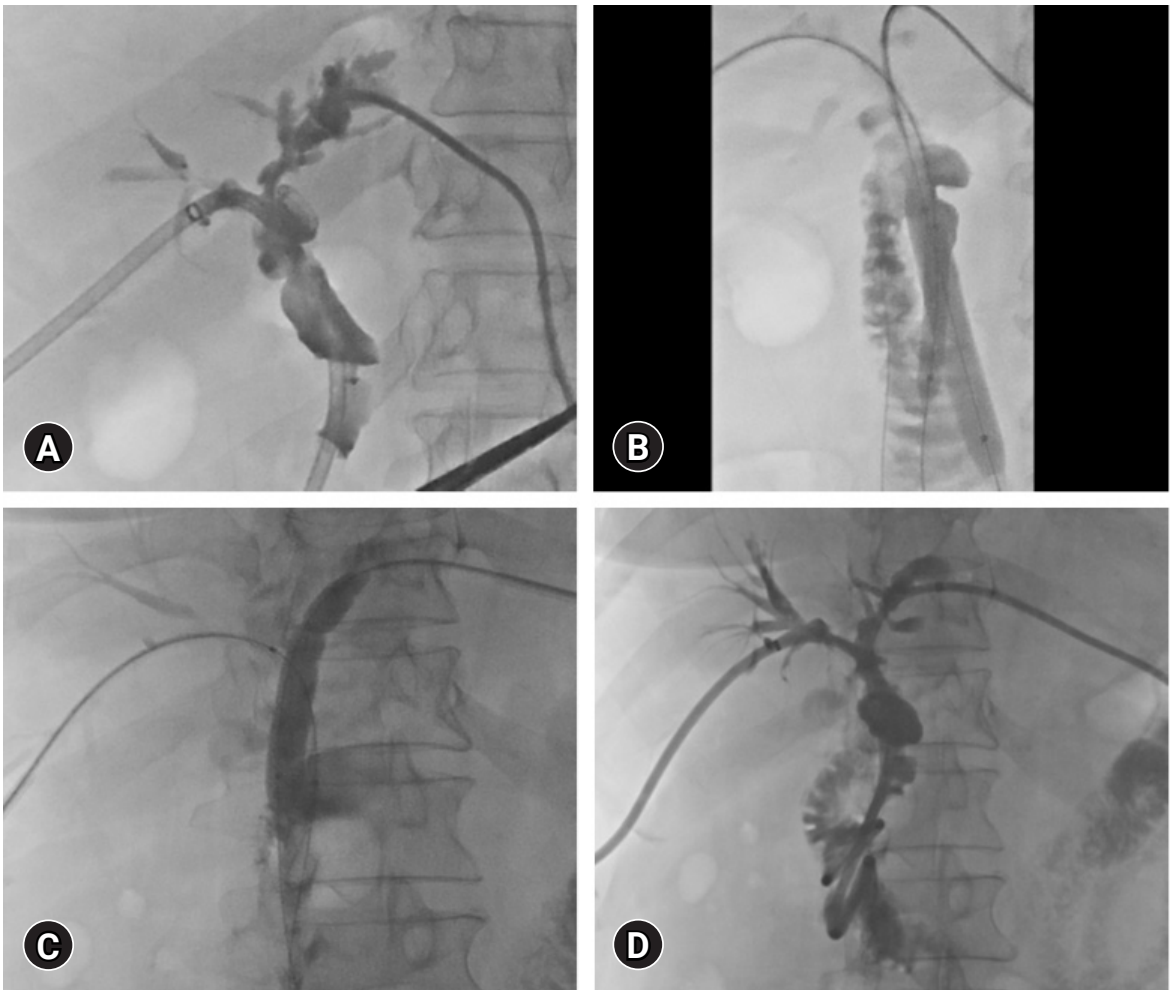

Fig. 4. The second balloon dilatation of the biliary stricture. (A) Tubogram shows the presence of residual strictures. (B, C) The second balloon dilatation of the intra- and extrahepatic stricture is extensively performed. (D) Tubogram shows improvement in multiple strictures.

The clinical diagnosis was ultimately determined to be congenital CBD web combined with multiple intrahepatic duct strictures.

The treatment plan was wait-and-see following balloon dilatation of the strictures. A tubogram through the left PTBD showed complete occlusion of the left hepatic duct (Fig. 3A). A right PTBD catheter was inserted and passed across the occlusion area at the hepatic hilum but was unable to cross the CBD web (Fig. 3B). After 4 days, the CBD web was finally penetrated by the guidewire, after which balloon dilatation of the intra- and extrahepatic strictures was conducted (Fig. 3C, 3D). The patient was then discharged with clamping of the two PTBD catheters and readmitted 1 month later. At this point, second extensive balloon dilatation of the intra- and extrahepatic strictures was performed through the right and left PTBD (Fig. 4). The patient was discharged again with clamping of the two PTBD catheters and readmitted 1 month later. A follow-up tubogram showed the good passage of the bile duct (Fig. 5). The two PTBD tubes were removed sequentially with close monitoring of liver function. The liver function test remained normal after PTBD removal, and hepatobiliary scintigraphy showed a 90-minute excretion rate of 82% without significant obstruction.

The patient has been doing well for 6 months after completion of the radiological intervention, with a 90-minute excretion rate of 80% on follow-up hepatobiliary scintigraphy (Fig. 6). Follow-up CT showed a thin doughnut-shaped web at the distal bile duct (Fig. 7). The patient was administered ursodeoxycholic acid (UDCA) to facilitate biliary drainage.

Discussion

The incidence of congenital webs of the extrahepatic ducts is reported to be very low, with approximately 20 cases being reported

 https://doi.org/10.12701/yujm.2021.01179

Fig. 5. Follow-up tubogram showing the good passage of the bile duct.

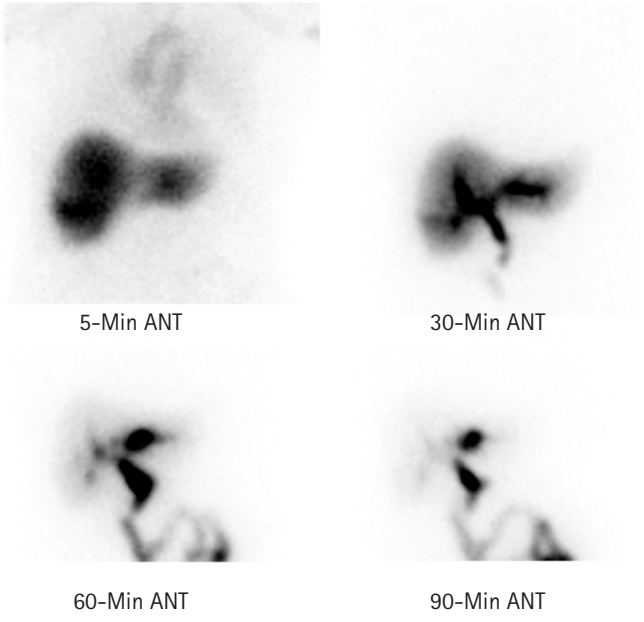

Fig. 6. Follow-up hepatobiliary scintigraphy taken at 6 months after the treatment showing a 90-minute excretion rate of 80% without significant obstruction. ANT, anterior view.

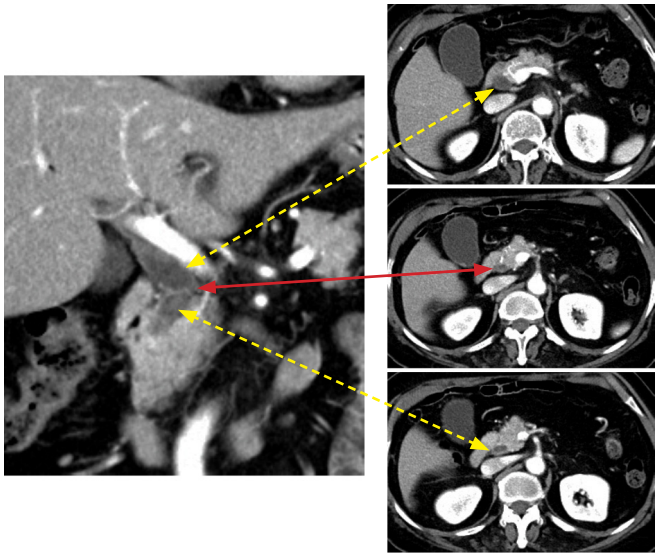

Fig. 7. Follow-up computed tomography taken at 6 months after the treatment showing a thin doughnut-shaped web at the distal bile duct. Dotted arrows indicate the proximal and distal levels of the bile duct to the web. Solid arrow indicates the level of a web at the distal bile duct.

in the literature [4-10]. The embryogenetic background of the biliary web appears to be similar to that of the septum of the stomach or intestine. During the early phase of embryonic development, the bile ducts pass through a solid stage with obliteration by epithelial concrescence or proliferation. During normal embryonic development, these solid structures become progressively vacuolated, forming the luminal structure of the bile duct system. If such recanalization occurs incompletely, it can be presented as congenital webs of the biliary system [4,6].

It is important to differentiate congenital webs from other causes of biliary stenosis. Biliary stenosis of iatrogenic causes is usually located in the CBD or right hepatic duct. Multiple intrahepatic and extrahepatic stenoses are often present in patients with primary sclerosing cholangitis [11,12]. Isolated biliary strictures are also known to be associated with blunt trauma to the abdomen, radiation therapy of the upper abdomen [13,14], and localized sclerosing cholangitis [11].

The physiological implication of a web of the biliary system may not be identical to the stenoses of the extrahepatic duct associated with other causes. Although the biliary web can induce symptomatic biliary obstruction, biliary drainage from the liver may remain undisturbed in the majority of patients. Patients may initially be asymptomatic or present with vague and nonspecific symptoms, such as abdominal pain, nausea, and vomiting. Early in the disease process, patients may only demonstrate elevations of transaminase and alkaline phosphatase levels along with ductal dilatation, without obstructive jaundice. Our patient also showed elevated liver enzymes and ductal dilatation without manifestation of obstructive jaundice. In clinical practice, overt obstructive jaundice occurs only after near-complete CBD obstruction, regardless of the cause of CBD obstruction.

A completely developed septum-inducing total biliary obstruction usually presents with obstructive jaundice soon after birth. If not treated effectively, this disease can lead to secondary biliary cir-

rhosis or even spontaneous perforation of the biliary system [15]. Delayed development of symptoms in adulthood is usually associated with incompletely formed or perforated webs, which cause only partial biliary obstruction. Our patient remained asymptomatic for over 70 years, likely because the biliary obstruction caused by the web was incomplete. The patient presented with multifocal biliary webs at the intrahepatic and extrahepatic bile ducts. Considering that the majority of the intrahepatic ducts were dilated, especially proximal to each biliary stricture, we presumed that multiple congenital webs had induced partial biliary obstruction for a long period. Finally, some symptoms of biliary obstruction occurred due to progressive deterioration of biliary drainage that was associated with the focal stricture-induced bottleneck phenomenon.

The majority of congenital biliary webs are associated with cholelithiasis or choledocholithiasis [9]. The association between congenital web and gallstone formation has not been clearly demonstrated. Congenital web-induced partial biliary obstruction can favor gallstone formation. However, an increased incidence of gallstone disease can lead to the diagnosis of asymptomatic webs that would not be diagnosed if gallstone disease is absent.

While standard imaging methods such as ultrasonography and CT may reveal bile duct dilatation, they are unlikely to reveal the presence of a biliary web. MRCP is useful for delineating the locations and shapes of the biliary webs. Congenital webs are usually not associated with malignancy. However, it is reasonable to resect this structure and obtain a frozen section biopsy prior to completing the procedure [10]. If a web is encountered during exploration of the extrahepatic biliary tree, it is necessary to perform an intraoperative cholangiogram to assess the rest of the ductal system to prevent inadvertent damage due to the association of these webs with other coexisting biliary anomalies. Surgical treatment was not indicated for our patient because of the presence of combined multiple biliary strictures, and the disease was clinically diagnosed as benign.

In a Japanese multicenter randomized trial that compared the CBD stone recurrence rate after bile duct stone removal, UDCA administration was shown to be an effective treatment for preventing CBD stone recurrence [16]. In a Chinese randomized clinical trial with liver transplant patients, UDCA treatment decreased the levels of serum ALT and AST during the 4 weeks after transplantation, and it also decreased the incidence of biliary sludge and casts within the first year. However, UDCA administration did not affect the overall outcomes up to 5 years after transplantation [17]. Although there is still some debate about its preventive effect on gallstone formation, we suggest the administration of UDCA in patients with a high risk of choledocholithiasis.

Congenital webs at the bile duct are very rare, and their treatment may vary depending on the patterns of biliary stenosis. Our experience suggests that radiological intervention with balloon dilatation can be a viable therapeutic option if surgical intervention is not indicated for congenital web and its associated disease.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization: SH; Data curation: HL, HH; Methodology, Visualization: SH, GYK; Writing-original draft: SH, HL; Writing-review & editing: all authros.

ORCID

Hanseul Lim, https://orcid.org/0000-0002-6128-855X
Shin Hwang, https://orcid.org/0000-0002-9045-2531
Gi-Young Ko, https://orcid.org/0000-0003-4617-1799
Hyejin Han, https://orcid.org/0000-0002-6091-1717

References

1. Lamah M, Dickson GH. Congenital anatomical abnormalities of the extrahepatic biliary duct: a personal audit. Surg Radiol Anat 1999;21:325–7.
2. Choi SH, Kim KW, Kwon HJ, Kim SY, Kwon JH, Song GW, et al. Clinical usefulness of gadoxetic acid-enhanced MRI for evaluating biliary anatomy in living donor liver transplantation. Eur Radiol 2019;29:6508–18.
3. Takeishi K, Shirabe K, Yoshida Y, Tsutsui Y, Kurihara T, Kimura K, et al. Correlation between portal vein anatomy and bile duct variation in 407 living liver donors. Am J Transplant 2015;15:155–60.
4. Furukawa H, Hara T, Taniguchi T. A case of septum formation of the common hepatic duct combined with an anomalous hepatic duct of the caudate lobe. Gastroenterol Jpn 1992;27:102–7.
5. Kato S, Nakagawa T, Kobayashi H, Arai E, Isetani K. Septum formation of the common hepatic duct associated with an anomalous junction of the pancreaticobiliary ductal system and

gallbladder cancer: report of a case. Surg Today 1994;24:534–7.
6. Dolar ME, Ates KB, Dalay AR, Caner ME, Sasmaz N, Sahin B. Congenital stricture of the common hepatic duct due to a web: an unusual case without jaundice. Hepatogastroenterology 1993;40:194–5.
7. Fisher MM, Chen SH, Dekker A. Congenital diaphragm of the common hepatic duct. Gastroenterology 1968;54:605–10.
8. Kottoor R, Alvares JF, Devarbhavi H. Successful endoscopic therapy of an obstructing common bile duct web. Gastrointest Endosc 2001;53:126–8.
9. Papaziogas B, Lazaridis C, Pavlidis T, Galanis I, Paraskevas G, Papaziogas T. Congenital web of the common bile duct in association with cholelithiasis. J Hepatobiliary Pancreat Surg 2002;9:271–3.
10. Margolis M, Schein M. Biliary web: a rare cause of extrahepatic biliary obstruction. Dig Surg 2001;18:317–9.
11. Gulliver DJ, Baker ME, Putnam W, Baillie J, Rice R, Cotton PB. Bile duct diverticula and webs: nonspecific cholangiographic features of primary sclerosing cholangitis. Am J Roentgenol 1991;157:281–5.
12. Panés J, Bordas JM, Bruguera M, Cortés M, Rodés J. Localized sclerosing cholangitis? Endoscopy 1985;17:121–2.
13. Yoon KH, Ha HK, Kim MH, Seo DW, Kim CG, Bang SW, et al. Biliary stricture caused by blunt abdominal trauma: clinical and radiologic features in five patients. Radiology 1998;207:737–41.
14. Cherqui D, Palazzo L, Piedbois P, Charlotte F, Duvoux C, Duron JJ, et al. Common bile duct stricture as a late complication of upper abdominal radiotherapy. J Hepatol 1994;20:693–7.
15. Shih SL, Lin JC, Lee HC, Blickman JG. Unusual causes of obstructive jaundice in children: diagnosis on CT. Pediatr Radiol 1992;22:512–4.
16. Yamamoto R, Tazuma S, Kanno K, Igarashi Y, Inui K, Ohara H, et al. Ursodeoxycholic acid after bile duct stone removal and risk factors for recurrence: a randomized trial. J Hepatobiliary Pancreat Sci 2016;23:132–6.
17. Wang SY, Tang HM, Chen GQ, Xu JM, Zhong L, Wang ZW, et al. Effect of ursodeoxycholic acid administration after liver transplantation on serum liver tests and biliary complications: a randomized clinical trial. Digestion 2012;86:208–17.

Case report

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):168-171
https://doi.org/10.12701/yujm.2021.01088

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Palisaded encapsulated neuroma on the lower lip: a case report

Jung Eun Seol[1,2], Seong Min Hong[1], Sang Woo Ahn[1], Jong Uk Kim[1], Woo Jung Jin[1], So Hee Park[1], Hyojin Kim[1]

[1]Department of Dermatology, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, Korea
[2]Cardiovascular and Metabolic Disease Center, Inje University, Busan, Korea

Palisading encapsulated neuroma is a rare, benign, cutaneous nerve sheath tumor. It usually occurs as an asymptomatic solitary skin-colored papule and commonly affects the nose and cheeks. Sometimes, it involves other sites, including the shoulder, upper arm, and trunk, but rarely involves the oral mucosa, including that of the lip. In our case, a 63-year-old female patient complained of a pinkish rubbery nodule on her lower lip. Histopathologic examination demonstrated a well-circumscribed nodule encapsulated by connective tissue stroma in the dermis. The nodule consisted of palisading spindle-shaped tumor cells with wavy and basophilic nuclei. The cells were arranged in streaming fascicles with multiple clefts and were strongly positive for S-100 proteins. To our knowledge, only three cases of palisading encapsulated neuroma on the lower lip have been reported in the Korean literature. Herein, we report a rare case of an oral palisaded encapsulated neuroma.

Keywords: Lip; Nerve sheath neoplasms; Neuroma

Introduction

Palisaded encapsulated neuroma (PEN) or solitary circumscribed neuroma is a benign neural tumor first described by Reed et al. [1] in 1972. It mainly occurs as a single, asymptomatic papule or nodule that slowly grows on the face of a middle-aged adult, and rarely occurs in the oral cavity, shoulder, trunk, limbs, etc. [2]. Histopathologic examination reveals an encapsulated dermal nodule comprised of proliferating Schwann cells and axons arranged in bundles. A total of three cases of PEN on the lips have been reported in South Korean literature [3-5]. It is assumed that this is due to the characteristic of PEN, which is asymptomatic and does not occur in the oral cavity. Herein, we report a rare case of PEN on the lips, along with a review of clinical and histological features.

Case

Ethical statesments: This study was approved by the Institutional Review Board (IRB) of Inje University Busan Paik Hospital (IRB No: BPH 2021-01-001). Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

A 63-year-old female patient presented with a cystic nodule on her lower lip. The lesion persisted for 6 months and gradually increased in size. The patient had no symptoms. She had a history of hypertension, for which she was taking oral medications. There was no significant family history or history of trauma to the lip.

Received: May 2, 2021 • **Revised:** June 8, 2021 • **Accepted:** June 15, 2021
Corresponding author: Hyojin Kim, MD, PhD
Department of Dermatology, Inje University Busan Paik Hospital, Inje University College of Medicine, 75 Bokji-ro, Busanjin-gu, Busan 47392, Korea
Tel: +82-51-890-6135 • Fax: +82-51-890-5845 • E-mail: derma09@hanmail.net

Physical examination revealed a solid and rubbery 0.4×0.4 cm nodule on her lower lip (Fig. 1). The nodule was completely excised, and biopsy was performed. Histological examination revealed a nodular tumor in the dermis. The tumor was well-circumscribed and partially encapsulated by fibrous connective tissue (Fig. 2A). Spindle-shaped cells were clustered inside the tumor, and the fascicles of spindle cells were separated by prominent clefts. There was no Verocay body formation, pleomorphism, or mitotic activity (Fig. 2B). On immunohistochemical examination, except for the connective tissue of the capsule, the tumor cells showed a positive reaction to S-100 proteins (Fig. 2C, 2D) and focally positive to neurofilament proteins (Fig. 2E). The above clinical and histological findings led to the diagnosis of PEN. No recurrence was observed after the complete excision.

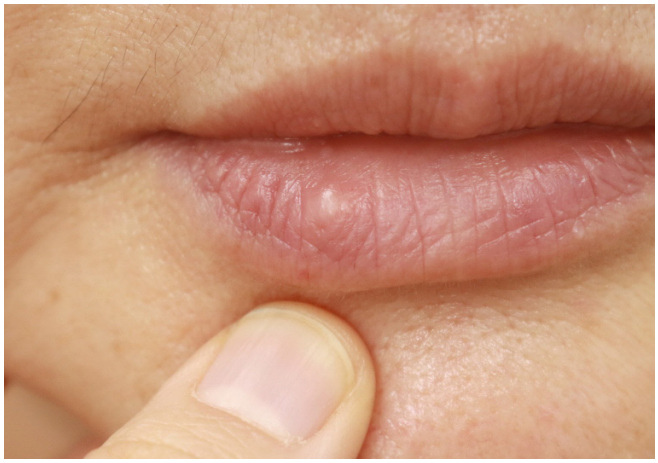

Fig. 1. Clinical photograph revealing a 0.4×0.4 cm solitary pinkish nodule on the lower lip.

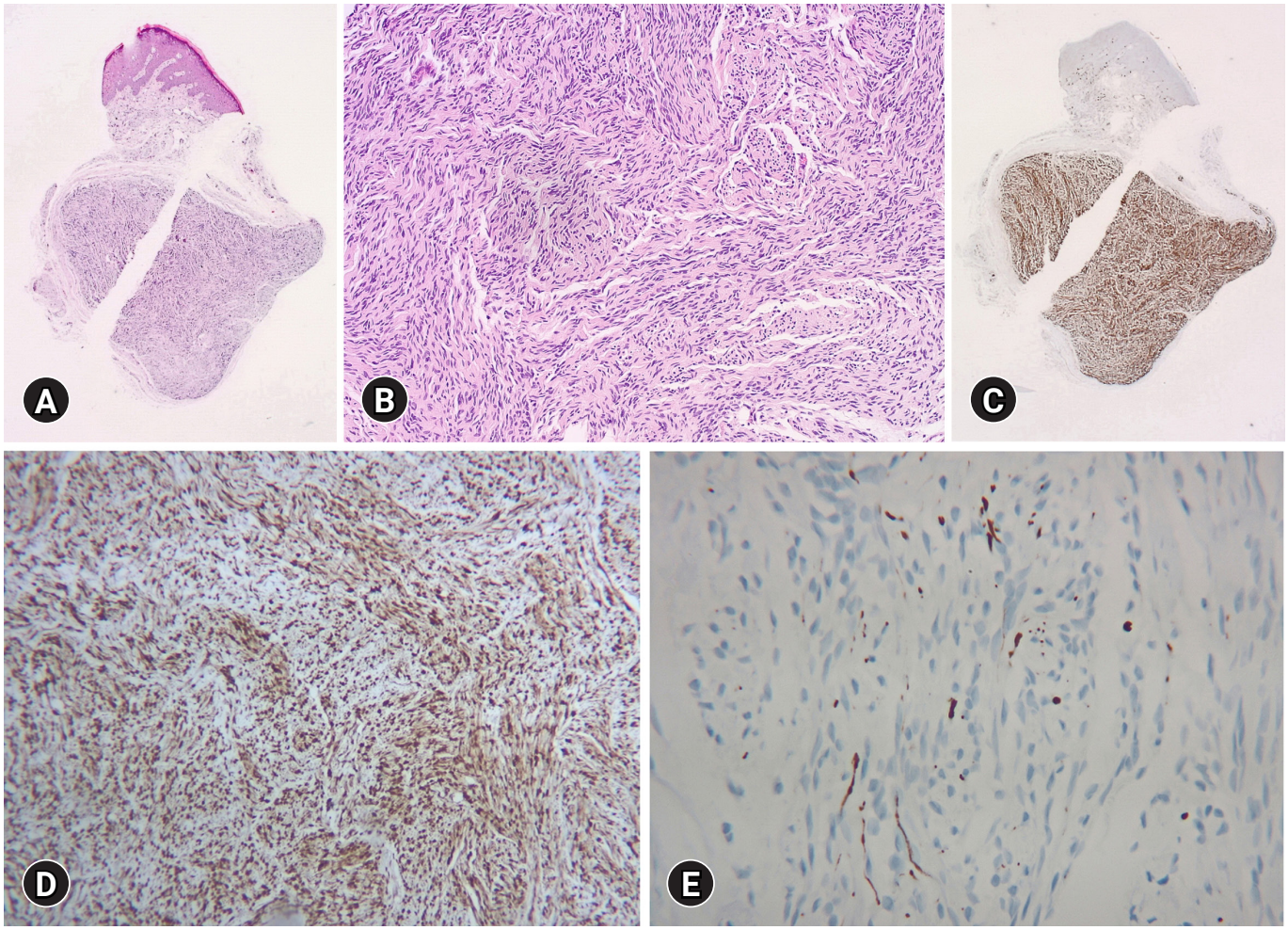

Fig. 2. (A) Histopathologic examination of the lower lip tissue shows a well-circumscribed nodule encapsulated by connective tissue stroma in the dermis (hematoxylin and eosin [H&E] stain, ×12.5). (B) The nodule consists of palisading spindle-shaped tumor cells with wavy, basophilic nuclei arranged as streaming fascicles and separated by clefts (H&E stain, ×100). (C, D) The tumor cells are strongly positive for S-100 proteins (immunohistochemical stain, [C] ×12.5, [D] ×100). (E) Neurofilament protein staining is focally positive within spindle cell fascicles, indicating the presence of axons (immunohistochemical stain, ×100).

Discussion

PEN is a benign neurogenic tumor that was first described by Reed et al. [1] in 1972. They categorized benign neurogenic tumors into three types; schwannomas, neurofibromas, and neuromas. PEN is a type of neuroma characterized by spindle-shaped cells arranged in a palisading pattern and surrounded by a connective tissue capsule [1]. Clinically, PEN appears as pinkish papules or nodules in middle-aged adults, with no sex predilection [6]. It originates from the peripheral nerves of the skin; therefore, it can occur in all areas where these nerves are distributed. However, in most cases, it occurs on the face over the cheeks and nose. It rarely occurs on the trunk, penis, extremities, and oral cavity, including the lips [7-9]. PEN accounts for approximately 25% of the nerve sheath tumors in the skin. However, it accounts for 11% of nerve sheath tumors in the oral cavity, of which 10% to 16% occur on the lips [2,10]. PEN usually does not cause symptoms such as itching or pain and enlarges over several years.

Pathologically, it is characterized by round or oval nodules with a capsule composed of thin collagen fibers. In the nodule, spindle-shaped cells form bundles with irregular rows. Immunohistochemical examination shows that the capsule is partially positive for epithelial membrane antigen, suggesting that it is derived from peripheral nerves, and the cells in the nodule are positive for S-100 proteins [11]. In our case, the results of immunohistochemical staining were consistent with those of PEN. Some cases of similar lesions with unclear palisading alignment or capsule formation have been reported, and researchers have proposed calling them "solitary circumscribed neuroma" instead of PEN [12]. In the 2013 and 2020 World Health Organization (WHO) classification of tumors of soft tissue and bone, solitary circumscribed neuroma is described as a formal name, and PEN is described as a synonym. However, even after the WHO classification was published, these terms have been used interchangeably [13,14].

The pathogenesis of PEN remains controversial. Reed et al. [1] suggested that PEN is a part of multiple endocrine neoplasia syndrome type 2. However, further research confirmed that the similarity in the clinical characteristics of PEN and the neuroma in multiple endocrine neoplasia syndrome type 2 was a coincidence in the case described by Reed et al. [1], and that the clinical characteristics of the two neuromas in other cases have shown many differences [2]. Recently, PEN has been accepted as a regenerative tumor secondary to trauma [7,15]. The morphological and cellular distributions of PEN and traumatic neuroma are found to be similar. Leblebici et al. [9] reported that PEN shows an increase in small-diameter peripheral nerve fibers similar to that in traumatic neuroma around the lesion. The lip is frequently damaged by teeth or food unconsciously; hence, we thought that this minor trauma might have led to the occurrence of PEN in our case.

Clinicopathologically, PEN in the oral cavity can be differentiated from neurofibroma, traumatic neuroma, and Schwann cell tumors. Unlike PEN, a neurofibroma does not have a capsule, the tumor cells are scattered, and a palisading pattern is not observed [13]. A traumatic neuroma appears after a history of trauma and is commonly accompanied by pain, burning sensation, or paresthesia. Additionally, infiltration of inflammatory cells around or inside the tumor cells can help differentiate a traumatic neuroma from PEN [16,17]. Although a Schwann cell tumor is surrounded by a capsule similar to that in PEN, it does not contain axons in the intracapsular part; therefore, it shows negative immunohistochemical staining for neural filaments, and the Antoni type A and B tissue is an important differentiation point.

PEN is usually treated by simple excision and rarely grows again, even after partial excision. Initially, our provisional diagnosis was a mucocele, which is a common asymptomatic lesion of the lip having a color similar to that of the mucosa. Although oral neural neoplasms are uncommon, they should be included in the differential diagnosis, and an accurate diagnosis should be made after an immunohistochemical examination.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization; HK, SHP; Supervision HK; Investigation; JES, SMH; Formal analysis: SWA, JUK, WJJ; Writing-original draft: JES, SMH; Writing-review & editing: SWA, JUK, WJJ, SHP, HK.

ORCID

Jung Eun Seol, https://orcid.org/0000-0002-3029-9635
Seong Min Hong, https://orcid.org/0000-0002-8273-7350
Sang Woo Ahn, https://orcid.org/0000-0001-8430-0323
Jong Uk Kim, https://orcid.org/0000-0003-4820-3870
Woo Jung Jin, https://orcid.org/0000-0003-4499-8901
So Hee Park, https://orcid.org/0000-0002-9600-799X
Hyojin Kim, https://orcid.org/0000-0003-0987-4938

References

1. Reed RJ, Fine RM, Meltzer HD. Palisaded, encapsulated neuromas of the skin. Arch Dermatol 1972;106:865–70.
2. Koutlas IG, Scheithauer BW. Palisaded encapsulated ("solitary circumscribed") neuroma of the oral cavity: a review of 55 cases. Head Neck Pathol 2010;4:15–26.
3. Cho YH, Lee JH, Bang DS, Kim YC. A case of palisaded encapsulated neuroma of the lower lip. Korean J Dermatol 2002;40:1552–6.
4. Cho DY, Kim DH, Choi KC, Chung BS. A case of palisaded encapsulated neuroma of the lower lip. Ann Dermatol 2006;18:37–9.
5. Lee SW, Yi JY, Cho BK, Houh W, Kim TY, Song KY. Palisaded encapsulated neuroma. Ann Dermatol 1990;2:136–40.
6. Manchanda AS, Narang RS, Puri G. Palisaded encapsulated neuroma. J Orofac Sci 2015;7:136–9.
7. Dover JS, From L, Lewis A. Palisaded encapsulated neuromas: a clinicopathologic study. Arch Dermatol 1989;125:386–9.
8. Val-Bernal JF, Alvarez-Cañas C, Vega A. Palisaded encapsulated neuroma of the glans penis. Urology 1995;45:689–91.
9. Leblebici C, Savli TC, Yeni B, Cin M, Aksu AE. Palisaded encapsulated (solitary circumscribed) neuroma: a review of 30 cases. Int J Surg Pathol 2019;27:506–14.
10. Dakin MC, Leppard B, Theaker JM. The palisaded, encapsulated neuroma (solitary circumscribed neuroma). Histopathology 1992;20:405–10.
11. Megahed M. Palisaded encapsulated neuroma (solitary circumscribed neuroma): a clinicopathologic and immunohistochemical study. Am J Dermatopathol 1994;16:120–5.
12. Fletcher CD. Solitary circumscribed neuroma of the skin (so-called palisaded, encapsulated neuroma): a clinicopathologic and immunohistochemical study. Am J Surg Pathol 1989;13:574–80.
13. Scolyer RA, Ferguson PM. Solitary circumscribed neuroma. In: The WHO Classification of Tumours Editorial Board, editor. WHO classification of tumours. Soft tissue and bone tumours. 5th ed. Lyon: IARC Press; 2020. p. 245-6.
14. Kutzner H. Solitary circumscribed neuroma. In: Fletcher CD, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO classification of tumours of soft tissue and bone. 4th ed. Lyon: IARC Press; 2013. p. 181-2.
15. Argenyi ZB, Santa Cruz D, Bromley C. Comparative light-microscopic and immunohistochemical study of traumatic and palisaded encapsulated neuromas of the skin. Am J Dermatopathol 1992;14:504–10.
16. Lopes MA, Vargas PA, Almeida OP, Takahama A, León JE. Oral traumatic neuroma with mature ganglion cells: a case report and review of the literature. J Oral Maxillofac Pathol 2009;13:67–9.
17. Maharudrappa B, Kumar GS. Neural tumours of oral and para oral region. Int J Dent Clin 2011;3:34–43.

Case report

eISSN 2799-8010
J Yeungnam Med Sci 2022;39(2):172-177
https://doi.org/10.12701/yujm.2021.01354

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Reverse Takotsubo cardiomyopathy with left bundle branch block after anesthesia induction in a patient with subarachnoid hemorrhage: a case report

Eun Kyung Choi[1], Jong-Hoon Kim[2], Minhyun Kim[1]

[1]Department of Anesthesiology and Pain Medicine, Yeungnam University College of Medicine, Daegu, Korea
[2]Department of Neurosurgery, Yeungnam University College of Medicine, Daegu, Korea

Takotsubo or reverse Takotsubo cardiomyopathy is a well-known cardiac complication of subarachnoid hemorrhage (SAH) that shows transient left ventricular wall motion abnormalities with electrocardiogram (ECG) changes. ST change followed by T inversion is a common ECG finding complicated with these disorders, left bundle branch block (LBBB) may be a potential ECG pattern which is seen. In this case, we describe the clinical profile and outcomes of a patient with LBBB and reverse Takotsubo cardiomyopathy after anesthetic induction, which was scheduled as an emergent external ventricular drainage after SAH. This is the first report of an LBBB pattern in reverse Takotsubo cardiomyopathy.

Keywords: Anesthesia; Bundle-branch block; Electrocardiography; Subarachnoid hemorrhage; Takotsubo cardiomyopathy

Introduction

Takotsubo cardiomyopathy is a well-known cardiac complication of subarachnoid hemorrhage (SAH). This disorder shows transient left ventricular wall motion abnormalities with electrocardiogram (ECG) changes in the absence of coronary artery disease [1]. Reverse Takotsubo cardiomyopathy is a variant of Takotsubo cardiomyopathy that presents a little different characteristic profile [2]. Takotsubo cardiomyopathy is characterized by transient left ventricular dysfunction with hypocontractile apex and compensatory hypercontractile base. On the other hand, reverse Takotsubo cardiomyopathy shows the opposite left ventricular movement, that is, a hypokinetic basal ventricular segment with a hyperkinetic apical contraction. In the ECG changes, although ST change followed by T inversion is a common ECG finding complicated with Takotsubo or reverse Takotsubo cardiomyopathy, left bundle branch block (LBBB) may be a potential ECG pattern which is seen [3]. In addition, LBBB has been considered a mortality predictor in patients with acute coronary artery disease [4,5]. To our knowledge, no studies have reported on reverse Takotsubo cardiomyopathy with LBBB after SAH. Therefore, we describe the clinical profile and outcomes of a patient with LBBB and reverse Takotsubo cardiomyopathy during surgery.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC-2021-08-034), and written informed consent was obtained from the patient.

Received: July 26, 2021 • **Revised:** September 2, 2021 • **Accepted:** September 7, 2021
Corresponding author: Eun Kyung Choi, MD, PhD
Department of Anesthesiology and Pain Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-620-3361 • Fax: +82-53-626-5275 • E-mail: ekchoe@ynu.ac.kr

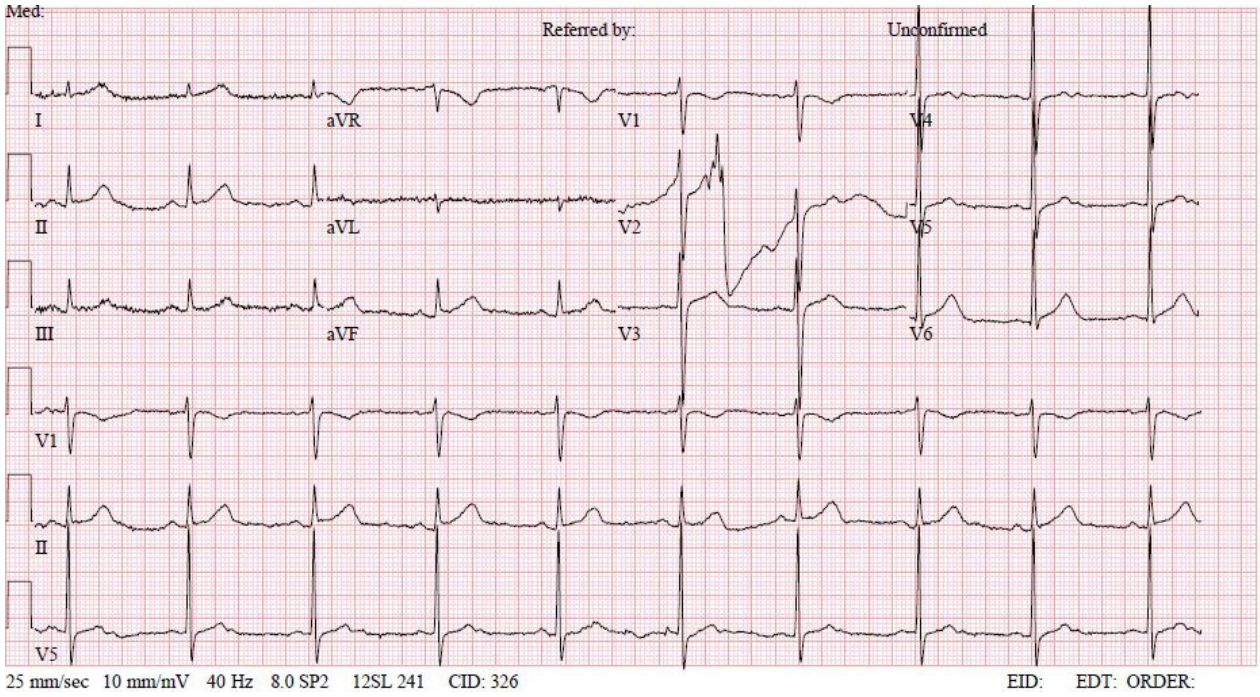

Fig. 1. Preoperative electrocardiogram with normal sinus rhythm.

A 50-year-old male (height, 172 cm; weight, 65 kg) with a history of SAH was presented to the emergency department with hydrocephalus after endovascular embolization by a ruptured subarachnoid aneurysm. He was scheduled for urgent external ventricular drainage catheterization. The patient had no cardiac symptoms, and ECG showed a normal sinus rhythm (NSR) (Fig. 1). Troponin-I was measured at 0.05 ng/mL, which was not significantly different from one year previously. Besides this, preoperative laboratory investigations were normal.

In the operating room, the patient's ECG was NSR at 70 beats/min. General anesthesia was induced with 90-mg propofol, continuous infusion of remifentanil, and 70-mg rocuronium. Due to insufficient NPO time, tracheal intubation was performed with rapid sequence induction. Immediately after tracheal intubation, the patient showed a blood pressure of 170/90 mmHg with a heart rate of 95 beats/min. Anesthesia was maintained with sevoflurane at 1.5 to 2.0 volume% in 50% oxygen in air with a continuous infusion of remifentanil (0.05–0.1 μg/kg/min). Approximately 10 minutes after tracheal intubation, during the surgeon draping the surgery site for hematoma evacuation and ventricular drainage, the ECG pattern suddenly changed from NSR to LBBB with wide QRS and was noted continuously (Fig. 2). After the operation was halted, a catheter was inserted into the radial artery for continuous hemodynamic monitoring. At that time, portable transthoracic echocardiogram (TTE) showed a depressed left ventricular ejection fraction (LVEF, 36%) (Fig. 3) while the left ventricular basal and mid segments were severely hypokinetic, while the apical segment was hyperkinetic (Table 1). The right ventricle and valve function were normal. Nonetheless, the patient was not administered hemodynamic support or catecholamine due to stable vital signs; mean arterial pressure (85–90 mmHg) and heart rate (70–80 beats/min) were not significantly different from before ECG changes. Based on the TTE findings and ECG changes, we diagnosed the reverse Takotsubo cardiomyopathy with LBBB. After consultation with an anesthesiologist, neurosurgeon, and caregiver we decided to continue the surgery. Twenty-five minutes after the ECG changes, the patient's ECG returned to NSR immediately after trephination. TTE showed mildly improved LVEF (44%) (Fig. 4) with mild hypocontractility of the basal segment (Table 1). Postsurgery, the patient was moved to the intensive care unit (ICU) and was intubated to prevent hemodynamic instability.

In the ICU, regional wall motion abnormality at the apical middle area was observed and the LVEF was 40% at bedside TTE. Troponin-I was then measured at 0.44 ng/mL. On postoperative day 1, a follow-up TTE revealed normal left ventricular wall motion and an LVEF of 63%. The troponin level also decreased steadily, reaching 0.05 ng/mL on postoperative day 3.

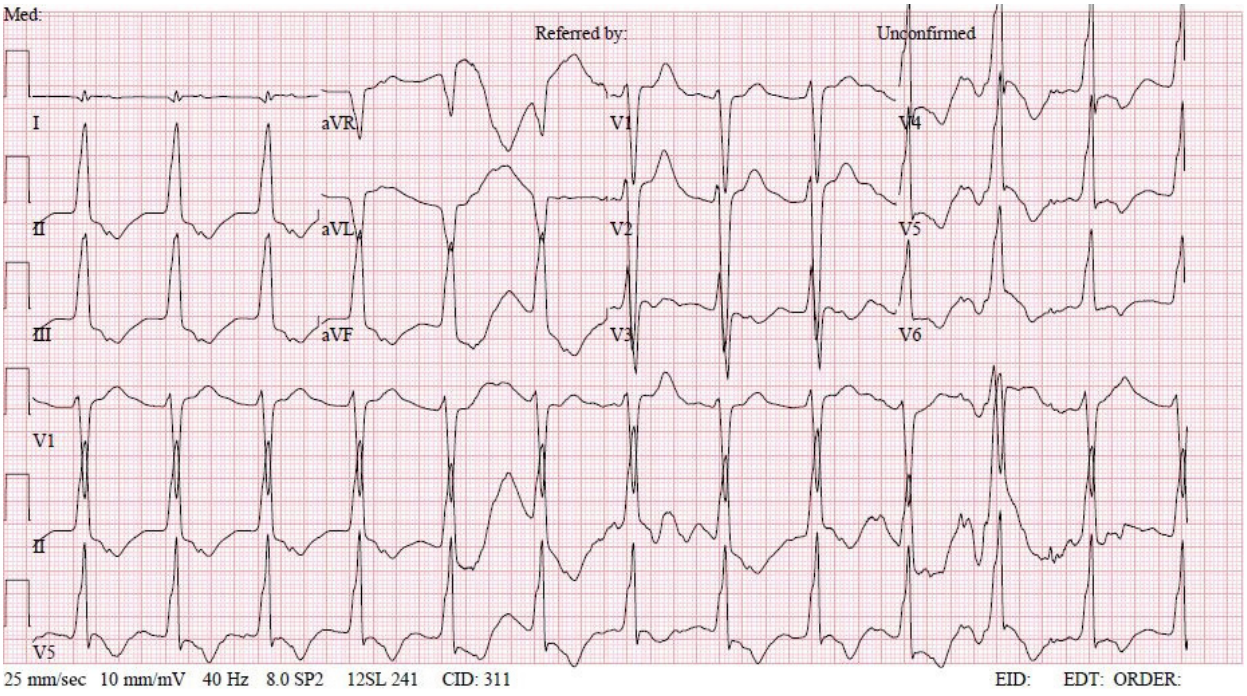

Fig. 2. Intraoperative electrocardiogram with left bundle branch block.

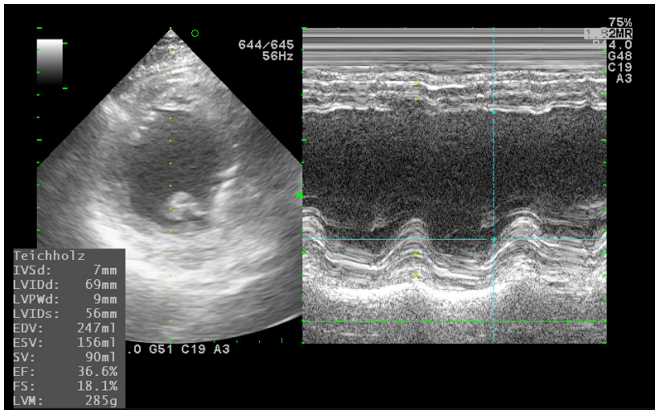

Fig. 3. Intraoperative transthoracic echocardiogram at the left bundle branch block. IVSd, interventricular septum diastolic; LVIDd, left ventricular internal dimension in diastole; LVPWd, left ventricular posterior wall thickness in diastole; LVIDs, left ventricular internal dimension in systole; EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; EF, ejection fraction; FS, fractional shortening; LVM, left ventricular mass.

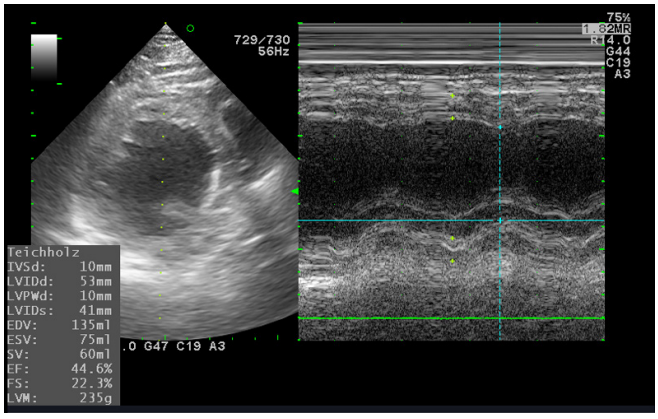

Fig. 4. Intraoperative transthoracic echocardiogram at the normal sinus rhythm. IVSd, interventricular septum diastolic; LVIDd, left ventricular internal dimension in diastole; LVPWd, left ventricular posterior wall thickness in diastole; LVIDs, left ventricular internal dimension in systole; EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; EF, ejection fraction; FS, fractional shortening; LVM, left ventricular mass.

Table 1. Transthoracic echocardiogram (TTE) findings

Variable	Intraoperative TTE	
	Sudden change to LBBB	Convert to NSR
Estimated LVEF	36%	44%
Left ventricular RWMA	Basal and mid segments - severe hypokinetic Apical segment - hyperkinetic	Basal segment - mild hypokinetic
Valvular state (stenosis/regurgitation)	Non-specific	Non-specific

LBBB, left bundle branch block; NSR, normal sinus rhythm; LVEF, left ventricular ejection fraction; RWMA, regional wall motion abnormality.

 https://doi.org/10.12701/yujm.2021.01354

Discussion

In this case, we present a patient who developed reverse Takotsubo cardiomyopathy with LBBB after anesthetic induction, which was scheduled as an emergent surgery for brain catheterization after SAH.

Takotsubo cardiomyopathy is a disorder characterized by acute coronary syndrome as follows: ECG change, elevation of cardiac biomarker, and left ventricular wall motion abnormalities not contributing to obstructive coronary disease [1]. More recently, reverse Takotsubo cardiomyopathy has been identified as a variant of Takotsubo cardiomyopathy [2]. The prevalence of reverse Takotsubo cardiomyopathy is lower than that of Takotsubo cardiomyopathy (2.2% vs. 82%) [6]. Takotsubo cardiomyopathy is characterized by transient left ventricular dysfunction with a hypocontractile apex with a compensatory hypercontractile base. While reverse Takotsubo cardiomyopathy shows the opposite left ventricular movement, in other words, a hypokinetic basal ventricular segment with a hyperkinetic apical contraction [2]. The difference in regional wall motion abnormalities between both has been speculated to be the distribution pattern of adrenergic receptors and variations in individual susceptibilities to catecholamine stimulation within the myocardium [7]. This speculation is also supported by differences in age and sex prevalence. In terms of age, adrenoreceptors are more abundant at the base in the younger population, which favors the development of reverse Takotsubo cardiomyopathy [1]. Conversely, Takotsubo cardiomyopathy is more prevalent in postmenopausal age with an abundance of adrenoreceptors at the apex [8]. Moreover, Takotsubo cardiomyopathy has a female predominance [9], while reverse Takotsubo cardiomyopathy showed an increased incidence in men up to 70% [10].

These clinical syndromes can occur partly due to emotional or physical stress [11]. During the perioperative period, various stresses including anxiety, surgical and anesthetic procedures, and inadequate analgesia can trigger Takotsubo or reverse Takotsubo cardiomyopathy [12,13]. Reverse Takotsubo cardiomyopathy is more often associated with triggering stressors than Takotsubo cardiomyopathy [1,10]. The catecholamine surge caused by these intense stresses has been considered as the main pathophysiologic mechanism of transient left ventricular dysfunction, which leads to multivessel coronary vasospasm, microvascular dysfunction, and subsequently myocardial stunning with contraction band necrosis [14]. In this case, our patient developed a sudden ECG change (LBBB with wide QRS) with left ventricular dysfunction (LVEF, 33% with hypokinetic basal and mid segments) after anesthetic induction, and returned to NSR ECG with mildly improved left ventricular function (LVEF, 46%) immediately after ventricular drainage. We speculate that the patient's physical stress from the induction of anesthesia, such as laryngoscopy, intravenous, and inhalational anesthetics as well as the patient's condition of SAH, as a medical stressor, triggered reverse Takotsubo cardiomyopathy. In addition, decompression of increased intracranial cerebral pressure by trephination may affect the conversion of sudden ECG changes (from LBBB to NSR) with mildly improved left ventricular dysfunction.

Among stress-induced cardiomyopathy, SAH has been well recognized as a priori draw (triggering stressor). Secondary cardiomyopathy has been found in 20% to 30% of patients with SAH [15]. High levels of catecholamines in SAH support the main pathophysiology of adrenergic storms, explaining Takotsubo cardiomyopathy or reverse Takotsubo cardiomyopathy. Reverse Takotsubo cardiomyopathy is more common in patients following SAH [16]. The difference of prevalence in patients with SAH seems to be explained by the left ventricle basal segment potentially being more vulnerable to catecholamine toxicity under neurogenic stress as this area has more sympathetic nerve endings, while the apex may be more vulnerable to catecholamine toxicity under general stress as the apex segment has more adrenoreceptors [17]. In a meta-analysis of patients with SAH, stress cardiomyopathy showed poor outcomes and increased mortality [18]; however, myocardial dysfunction is independent of SAH severity [19]. In this case, the patient's condition of SAH was preceded by both surgery and anesthetic stressors, and the patient had no previous history of cardiac disease.

Takotsubo cardiomyopathy is characterized by ischemic ECG changes (either ST-segment elevation and/or T-wave inversion). In some cases, although uncommon, LBBB has been noted as the ECG pattern of Takotsubo cardiomyopathy presentation. Parodi et al. [3] showed a trend towards a poor baseline clinical profile, such as more severe left ventricular systolic dysfunction and delayed left ventricular functional recovery among patients with Takotsubo cardiomyopathy presenting with LBBB. Moreover, on long term follow-up, the patients showed a higher mortality rate than those without LBBB. However, after adjusting for age and baseline properties, LBBB was not found to be an independent predictor of poor outcomes. In reverse Takotsubo cardiomyopathy, the ECG pattern is less understood than that of Takotsubo cardiomyopathy. Elikowski et al. [20] reported that ST segment depression is a more common abnormality; however, ST changes may be absent in the course of reverse Takotsubo cardiomyopathy with intracranial hemorrhage. In our case, we observed ECG changes in the LBBB along with left ventricular dysfunction. To our knowledge, this is the first report of an LBBB pattern in reverse Takotsubo cardiomyopathy. This suggests that any ECG pattern that exhib-

its evidence of LV dysfunction, as well as the classic form, can be observed in reverse Takotsubo cardiomyopathy. Moreover, LBBB may represent the early ECG phase in reverse Takotsubo cardiomyopathy. Therefore, in case of ECG changes after SAH are incompatible with coronary artery syndrome, Takotsubo cardiomyopathy or reverse Takotsubo cardiomyopathy should be considered as a differential diagnosis. Moreover, as with patients with Takotsubo cardiomyopathy with LBBB, the presence of LBBB in patients with reverse Takotsubo cardiomyopathy may not be an independent predictor of poor outcomes. However, since LBBB has been considered a mortality predictor in patients with acute coronary artery disease [4,5], more cases will need to be evaluated for the assessment of outcomes in reverse Takotsubo cardiomyopathy.

In conclusion, we describe a case of unexpected reverse Takotsubo cardiomyopathy with an LBBB ECG pattern during surgery in a patient with SAH. This case enhances our knowledge of ECG characteristics in reverse Takotsubo cardiomyopathy.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author contributions

Conceptualization, Project administration, Investigation, Supervision: EKC; Data curation, Formal analysis, Resources: MHK; Methodology: EKC, JHK; Visualization: JHK, Writing-original draft: EKC; Writing-review & editing: JHK.

ORCID

Eun Kyung Choi, https://orcid.org/0000-0001-5758-6741
Jong-Hoon Kim, https://orcid.org/0000-0001-9492-6901
Minhyun Kim, https://orcid.org/0000-0001-8219-1071

References

1. Ramaraj R, Movahed MR. Reverse or inverted takotsubo cardiomyopathy (reverse left ventricular apical ballooning syndrome) presents at a younger age compared with the mid or apical variant and is always associated with triggering stress. Congest Heart Fail 2010;16:284–6.
2. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 2008;155:408–17.
3. Parodi G, Salvadori C, Del Pace S, Bellandi B, Carrabba N, Gensini GF, et al. Left bundle branch block as an electrocardiographic pattern at presentation of patients with Tako-tsubo cardiomyopathy. J Cardiovasc Med (Hagerstown) 2009;10:100–3.
4. Godman MJ, Lassers BW, Julian DG. Complete bundle-branch block complicating acute myocardial infarction. N Engl J Med 1970;282:237–40.
5. Brilakis ES, Wright RS, Kopecky SL, Reeder GS, Williams BA, Miller WL. Bundle branch block as a predictor of long-term survival after acute myocardial infarction. Am J Cardiol 2001;88:205–9.
6. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med 2015;373:929–38.
7. Mori H, Ishikawa S, Kojima S, Hayashi J, Watanabe Y, Hoffman JI, et al. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. Cardiovasc Res 1993;27:192–8.
8. Ramaraj R. Stress cardiomyopathy: aetiology and management. Postgrad Med J 2007;83:543–6.
9. Ramaraj R, Sorrell VL, Movahed MR. Levels of troponin release can aid in the early exclusion of stress-induced (takotsubo) cardiomyopathy. Exp Clin Cardiol 2009;14:6–8.
10. Song BG, Chun WJ, Park YH, Kang GH, Oh J, Lee SC, et al. The clinical characteristics, laboratory parameters, electrocardiographic, and echocardiographic findings of reverse or inverted takotsubo cardiomyopathy: comparison with mid or apical variant. Clin Cardiol 2011;34:693–9.
11. Roshanzamir S, Showkathali R. Takotsubo cardiomyopathy a short review. Curr Cardiol Rev 2013;9:191–6.
12. Yoshikawa T. Takotsubo cardiomyopathy, a new concept of cardiomyopathy: clinical features and pathophysiology. Int J Cardiol 2015;182:297–303.
13. Liu S, Bravo-Fernandez C, Riedl C, Antapli M, Dhamee MS. Anesthetic management of Takotsubo cardiomyopathy: general versus regional anesthesia. J Cardiothorac Vasc Anesth 2008;22:438–41.
14. Lindsay J, Paixao A, Chao T, Pichard AD. Pathogenesis of the Takotsubo syndrome: a unifying hypothesis. Am J Cardiol 2010;106:1360–3.
15. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. Circulation 2008;118:397–409.
16. Hravnak M, Frangiskakis JM, Crago EA, Chang Y, Tanabe M, Gorcsan J 3rd, et al. Elevated cardiac troponin I and relationship to persistence of electrocardiographic and echocardiographic abnormalities after aneurysmal subarachnoid hemorrhage.

Stroke 2009;40:3478–84.
17. Kristensen SL, Mogensen UM, Jhund PS, Petrie MC, Preiss D, Win S, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure with Preserved Ejection Fraction). Circulation 2017;135:724–35.
18. van der Bilt IA, Hasan D, Vandertop WP, Wilde AA, Algra A, Visser FC, et al. Impact of cardiac complications on outcome after aneurysmal subarachnoid hemorrhage: a meta-analysis. Neurology 2009;72:635–42.
19. Schuiling WJ, Dennesen PJ, Tans JT, Kingma LM, Algra A, Rinkel GJ. Troponin I in predicting cardiac or pulmonary complications and outcome in subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry 2005;76:1565–9.
20. Elikowski W, Małek-Elikowska M, Kudliński B, Skrzywanek P, Smól S, Rzymski S. ECG pattern in reverse takotsubo cardiomyopathy demonstrated in 5 cases with intracranial hemorrhage. Pol Merkur Lekarski 2016;41:136–40.

Instructions to authors

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Enactment December 30, 1984
First revision April 20, 2011
Second revision May 22, 2012
Third revision July 17, 2013
Fourth revision April 22, 2014
Fifth revised December 23, 2014
Sixth revised April 30, 2018
Seventh revised July 7, 2021
Recently revised December 10, 2021

Journal of Yeungnam Medical Science (JYMS), the official journal of Yeungnam University College of Medicine and Yeungnam University Institute Medical Science, is published four times a year (January 31, April 30, July 31, and October 31). The goal of the JYMS is to publish high quality manuscripts dedicated to clinical or basic research. Any authors affiliated with an accredited biomedical institution may submit manuscripts of editorials, review articles, original articles, case reports, image vignettes, communications, and imagery. Manuscripts are received with the understanding that they are not under simultaneous consideration by any other publications, and that the authors realize that the identities of the reviewers are kept confidential. The editors reserve the right to make corrections, both literary and technical, to the papers. The agreement of copyright transfer from all the authors should be sent with the manuscript submission. A copyright transfer form is available at the journal homepage.

Editorial policy

The editor assumes that all authors listed in a manuscript have agreed with the following policy of the JYMS on submission of manuscript. Except for the negotiated secondary publication, manuscript submitted to the journal must be previously unpublished and not be under consideration for publication elsewhere.

The purpose of editing is to improve the quality of the paper and to make it possible to convey the topic to readers as briefly as possible. Appropriate peer reviewers are selected to evaluate the creativity and scientific basis of the paper. We also determines the appropriateness of charts and figures. Submitted papers are first reviewed by the editorial committee and rejected if the form is inappropriate or the contents are inadequate.

Anyone who would like to submit a manuscript is advised to carefully read the aims and scope section of this journal. Manuscripts should be prepared for submission according to the Introduction to Authors. For issues not addressed in these instructions, the author is referred to the International Committee of Medical Journal Editors (ICMJE) "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" (http://www.icmje.org).

Compliance with ICMJE Recommendations: The journal adheres completely to the ethical guidelines and best practices published by professional organizations, including Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmje-recommendations.pdf) from ICMJE and Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by COPE, DOAJ, WAME, and OASPA; (http://doaj.org/bestpractice).

Ethical considerations

Research ethics

All of the manuscripts should be prepared based on strict observation of research and publication ethics guidelines recommended by the Council of Science Editors (http://www.councilscienceeditors.org), International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org), World Association of Medical Editors (WAME, http://www.wame.org), and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). All studies involving human subjects or human data must be reviewed and approved by a responsible Institutional Review Board (IRB). Please refer to the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) for all investigations involving human materials. Animal experiments also should be reviewed by an appropriate committee (IACUC) for the care and use of animals. Also studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (IBC). The approval should be described in the Methods section. For studies of humans including case reports and image vignettes, state whether informed consents were obtained from the study participants. The editor of JYMS may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. The JYMS will follow the guidelines

by the Committee on Publication Ethics (COPE, http://publicationethics.org) for settlement of any misconduct.

Conflicts of interest

The corresponding author of an article is asked to inform the Editor of the authors' potential conflicts of interest possibly influencing the research or interpretation of data. A potential conflicts of interest should be disclosed in the cover letter even when the authors are confident that their judgments have not been influenced in preparing the manuscript. Such conflicts may include financial support or private connections to pharmaceutical companies, political pressure from interest groups, or academic problems. Disclosure form shall be same with ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (http://www.icmje.org/coi_disclosure.pdf). The Editor will decide whether the information on the conflicts should be included in the published paper. In particular, all sources of funding for a study should be explicitly stated. The JYMS asks referees to let its editor know of any conflicts of interest before reviewing a particular manuscript.

Authorship

Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, and/or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Every author should meet all of these four conditions. After the initial submission of a manuscript, any changes whatsoever in authorship (adding author(s), deleting author(s), or re-arranging the order of authors) must be explained by a letter to the editor from the authors concerned. This letter must be signed by all authors of the paper. Copyright assignment must also be completed by every author.

- Corresponding author and first author: JYMS does not allow multiple corresponding authors for one article. Only one author should correspond with the editorial office and readers for one article. JYMS does accept notice of equal contribution for the first author when the study was clearly performed by co-first authors.
- Correction of authorship after publication: JYMS does not correct authorship after publication unless a mistake has been made by the editorial staff. Authorship may be changed before publication but after submission when an authorship correction is requested by all of the authors involved with the manuscript.

Originality, plagiarism and duplicate publication

Submitted manuscripts must not have been previously published or be under consideration for publication elsewhere. No part of the accepted manuscript should be duplicated in any other scientific journal without the permission of the Editorial Board. Submitted manuscripts are screened for possible plagiarism or duplicate publication by Similarity Check using 'Turnitin' program (iParadigms, LLC., Oakland, CA, USA) upon arrival. If plagiarism or duplicate publication is detected, the manuscripts may be rejected, the authors will be announced in the journal, and their institutions will be informed. There will also be penalties for the authors.

A letter of permission is required for any and all material that has been published previously. It is the responsibility of the author to request permission from the publisher for any material that is being reproduced. This requirement applies to text, figures, and tables.

Secondary publication

It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by International Committee of Medical Journal Editors (ICMJE), available from http://www.icmje.org. These are:

- The authors have received approval from the editors of both journals (the editor concerned with the secondary publication must have access to the primary version).
- The priority for the primary publication is respected by a publication interval negotiated by editors of both journals and the authors.
- The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
- The secondary version faithfully reflects the data and interpretations of the primary version.
- The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first reported in the (journal title, with full reference)"—and the secondary version cites the primary reference.
- The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the United States National Library of Medicine (NLM) does not consider translations as "republications" and does not cite or index them when the original article was published in a journal that is indexed in MEDLINE.

Registration of the clinical trial research

Clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" should be registered to the primary registry to be prior publication. JYMS accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/en/), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), ISRCTN Resister (www.ISRCTN.org), or the Clinical Research Information Service (CRIS), Korea CDC (https://cris.nih.go.kr/cris/index.jsp). The clinical trial registration number shall be published at the end of the abstract.

Data sharing statement

JYMS accepts the ICMJE Recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf). All manuscripts reporting clinical trial results should submit a data sharing statement following the ICMJE guidelines from 1 July 2018. Authors may refer to the editorial, "Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in JKMS Vol. 32, No. 7: 1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

Process to manage the research and publication misconduct

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of JYMS will discuss the suspected cases and reach a decision. JYMS will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

For the policies on research and publication ethics not stated in the Instructions, Guidelines on Good Publication (http://publicationethics.org) or Good Publication Practice Guidelines for Medical Journals (http://kamje.or.kr) can be applied.

Categories of publications

JYMS publishes editorials, review articles, original articles, case reports, image vignettes, communications, and imagery. Editorials are invited perspectives on an area of medical science, dealing with very active fields of research, current medical interests, fresh insights and debates. Review articles provide a concise review of a subject of importance to medical researchers written by an invited expert in medical science. Original articles are papers reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers. Case reports deal with clinical cases of medical interest or innovation. Image vignettes present state-of-the-art imaging that can be used in the evaluation of unusual clinical cases. Communications are interesting and instructive information for readers. Imagery is drawings, illustrations, or photographs of artistic and imaginative qualities of the readers.

Manuscript submission

The main document with manuscript text and tables should be prepared with a Microsoft Word program. Authors should submit manuscripts via the online submission system (https://submit.e-jyms.org). Please log in first as a member of the system and follow the directions. Manuscripts should be submitted by the corresponding author, who should indicate the address and phone number for correspondence in the title page of the manuscript. If available, a fax number and e-mail address would be helpful. The revised manuscript should be submitted through the same web system under the same identification numbers. Items pertaining to manuscripts submitted for publication, as well as letters or other forms of communication regarding the editorial management of JYMS, all correspondences and business communications should be sent to:

So-Young Park, MD, PhD, Editor-in-Chief
Journal of Yeungnam Medical Science
Yeungnam University College of Medicine
170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6832, Fax: +82-53-651-0394
E-mail: jyms@yu.ac.kr
Homepage: https://e-jyms.org

Peer review process

JYMS reviews all manuscripts received. A manuscript is previewed for its format and academic relevancy, and then rejected or sent to the 2 (or more) relevant investigators available for review of the contents. The editor selects peer referees by recommendation of the editorial board members or from the board's specialist database. The identities of the reviewers and authors will not be revealed (double blinded review). All the radiologic images and pathologic

(microscopic) images are reviewed by radiologist or pathologist for appropriateness. A manuscript containing statistical analysis will be reviewed by a statistical editor.

Upon completion of the review, authors will receive notification of the Editor's decision by e-mail with comments offered by the reviewers. Revised manuscripts must be submitted within 3 months of the date on the decision letter.

Acceptance of manuscripts is based on many factors, including the importance, originality, and priority of the research. Acceptance of the manuscript is decided based on the critiques and recommended decision of the referees. A referee may recommend "accept", "minor revision", "major revision", or "reject." If there is a marked discrepancy in the decisions between two referees or between the opinions of the author and referee(s), the editor may send the manuscript to another referee for additional comments and a recommended decision. The reviewed manuscripts are returned back to the corresponding author with comments and recommended revisions. Names and decisions of the referees are masked. A final editor's decision on acceptance or rejection for publication is forwarded to the corresponding author from the editorial office.

The usual reasons for rejection are topics that are too specific and target audience that is too limited, insufficient originality, serious scientific flaws, poor quality of illustrations, or absence of a message that might be important to readers. Rarity of a disease condition is itself not an acceptable justification for case report and image vignette. The peer review process takes usually 2–4 weeks after the manuscript submission.

Revisions are usually requested to take account of criticisms and comments made by referees. The revised manuscript should be resubmitted via the web system. Failure to resubmit the revised manuscript within 2 months without any notice from the corresponding author is regarded as a withdrawal. The corresponding author must indicate clearly what alterations have been made in response to the referee's comments point by point. Acceptable reasons should be given for noncompliance with any recommendation of the referees.

If the author disagrees with the editorial board's decision, he or she can apply for an objection through individual contact (e-mail, etc.).

Copyrights and creative commons attribution license

Manuscript preparation

Review article

All Review articles will undergo peer review. An abstract is required whereas Methods section and a Results section are not required (no more than 250 words). The length of review articles is limited to 5,000-8,000 words with a maximum of 100 references.

Original article

Original articles should begin with the title page followed by an abstract; a list of key words; an Introduction, Methods, Results, Discussion, References (up to 40 references), and tables and/or illustrations.

1) Title page

The tile page should contain the following information: (1) title (less than 150 characters, including spaces); (2) author list (first name, middle name, and last name); (3) name of the institutions at which the work was performed; (4) acknowledgement of research support; (5) name, address, telephone, fax number, and e-mail address of the corresponding author; (6) running title (less than 50 characters, including spaces).

2) Abstract

Abstract must be organized and formatted according to the following headings: Background, Methods, Results, and Conclusion. The abstract length is typically no more than 250 words.

3) Keywords

List 3-6 keywords from the list provided in Index Medicus under "Medical Subject Heading (MeSH)."

4) Text

The text of manuscripts must have the following sections: In-

troduction, Methods, Results, and Discussion. The body of the manuscript should be written as concisely as possible. All pages of the manuscript should be numbered.

Introduction

This should provide a context or background for the study and states the specific purpose or research objective of or hypothesis tested by the study. This may include mention of papers most closely related to the article, and of the problem.

Methods

Explanation of the experimental methods should be concise but sufficient to allow other workers to reproduce the results. This provides the technical information, apparatus (the manufacturer's name and brief address) and procedures. Give references and brief descriptions for the methods that have been published. Describe statistical methods with enough detail to enable a reader with access to the original data to verify the reported results. Define statistical terms, abbreviations, and most symbols.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Results

This should include a concise textual description of the data presented in tables and figures.

Discussion

This section includes the new and important aspects of the study and the conclusions. The data should be interpreted concisely. Speculation is permitted, but it must be supported by the data presented by the authors.

References

References should be numbered consecutively in the order in which they are first mentioned in the text, with numbers in square brackets before any closing punctuation. They should be listed on a separate document under the heading "References," and double-spaced. Reference format should conform to that set forth in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals. 5th ed." (JAMA 1997;277:927-34). Titles of journals should be abbreviated according to the Index Medicus style.

Reference style:

Journal articles

List all authors when six or less; when seven or more, list the first six and add et al.

Vega KJ, Pina I. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.

Verbalis JG. Renal physiology of nocturia. Neurourol Urodyn 2014;33(Suppl 1):S6-9.

Book

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

Luzikov VN. Mitochondrial biogenesis and breakdown. Galkin AV, translator; Roodyn DB, editor. New York: Consultants Bureau; 1985. p. 362

Book chapter

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Web resources

Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 [cited 2007 Jan 5];27:34-7. http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf

Testa J. The Thomson Reuters journal selection process [Internet]. Philadelphia: Thomson Reuters; 2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process

5) Tables

Tables should fit within a single page. The Table's legend may include any pertinent notes and must include definitions of all abbreviations and acronyms that have been used in the Table. For footnotes, the following symbols should be used in this sequence: a), b), c), d), e), f), g), h), etc. Authors are obligated to indicate the significance of their observations by appropriate statistical analysis.

6) Illustrations

Figures must be cited consecutively using Arabic numerals. Authors must submit illustrations as electronic files. Acceptable figure file formats are JPEG, TIFF, and PPT/PPTX. Each figure needs to be prepared in a resolution higher than 300 dpi with good contrast and sharpness. The file size of each submitted figure should not exceed 10 MB per figure. If the patient's photograph is presented in a paper, it should be manipulated to make it difficult to recognize. Patients introduced in the manuscripts should be informed and aware that their photographs, videotapes, and other images (imaging records) will be released by the authors, and the authors should attach the Authorization and Release Form available at the JYMS website (https://www.e-jyms.org/authors/ethics.php) including each patient's signature. If the patient is a minor, a written consent of the guardian must be submitted.

7) Legends for tables and illustrations

Typed legends that use double-spacing should start on a separate page with Arabic numerals corresponding to the Tables or Illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the Tables or Illustrations, they should be individually identified and explained clearly in the legend.

8) Abbreviations

Authors should limit the use of abbreviations to an absolute minimum. Abbreviations are not to be used in titles. Abstracts may contain abbreviations for terms mentioned many times in the abstract section, but each term must be identified the first time it is mentioned.

9) Unit of measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperature should be in degrees Celsius. Authors must consult the information for authors for the particular journal and should report laboratory information in both the local and International System of Units (SI).

Case report

Case reports should consist of an Abstract, Keywords, Introduction, Case, Discussion, and References (no more than 20). Case reports should have fewer than nine authors. The abstract should be concisely written (no more than 250 words).

Image vignette

Image vignette should be organized in the following sequence: a summary of the presentation, imaging features and discussion. No abstract is required for this manuscript. There should be no more than five references and no more than two figures. Total length should be no longer than 500 words (excluding figure legends, ethical statements, conflicts of interest, author contributions, ORCID, and references).

Communications

Although communication articles are not limited in the format, they should contain a self-standing abstract and references. The abstract should be concisely written and not exceed 250 words.

Imagery

This is a regular section of JYMS, featured at the beginning of issue and devoted to the artistic and imaginative qualities of the readers. JYMS invites your drawings, illustrations, or photographs with a brief explanation. Please send electronic images via e-mail to: jyms@yu.ac.kr. These contributions will not be returned.

Permission

If any portion of a manuscript has been previously published, the original source must be acknowledged, and the written permission from the copyright holder to reproduce the material must be submitted. It is the responsibility of the author to request permission from the publisher for any material that is being reproduced. This requirement applies to text, illustrations, and tables.

Article processing charges

Manuscripts that have accepted will be charged KRW 200,000 and the surcharge for color figures is none.

Author change

If the addition or deletion of authors or changes in the order of authorship is required, the correspondent author must complete the authorship change form and submit it to the editorial board with the signature of all existing authors and new authors. When there is a request for change by the author, the editorial committee convenes an ethics committee and judges whether it is appropriate. If a new author should be added or an author should be deleted after the submission, it is the responsibility of the corresponding author to ensure that all of the authors concerned are aware of and agree to the change in authorship. The JYMS has no responsibility for such changes.

Research and publication ethics

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Enactment May 22, 2012

Research ethics

All of the manuscripts should be prepared based on strict observation of research and publication ethics guidelines recommended by the Council of Science Editors (http://www.councilscienceeditors.org), International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org), World Association of Medical Editors (WAME, http://www.wame.org), and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). All studies involving human subjects or human data must be reviewed and approved by a responsible Institutional Review Board (IRB). Please refer to the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) for all investigations involving human materials. Animal experiments also should be reviewed by an appropriate committee (IACUC) for the care and use of animals. Also studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (IBC). The approval should be described in the Methods section. For studies of humans including case reports, state whether informed consents were obtained from the study participants. The editor of JYMS may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. The JYMS will follow the guidelines by the Committee on Publication Ethics (COPE, http://publicationethics.org) for settlement of any misconduct.

Conflicts of interest

The corresponding author of an article is asked to inform the Editor of the authors' potential conflicts of interest possibly influencing the research or interpretation of data. A potential conflicts of interest should be disclosed in the cover letter even when the authors are confident that their judgments have not been influenced in preparing the manuscript. Such conflicts may include financial support or private connections to pharmaceutical companies, political pressure from interest groups, or academic problems. Disclosure form shall be same with ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (http://www.icmje.org/coi_disclosure.pdf). The Editor will decide whether the information on the conflicts should be included in the published paper. In particular, all sources of funding for a study should be explicitly stated. The JYMS asks referees to let its editor know of any conflicts of interest before reviewing a particular manuscript.

Authorship

Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, and/or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Every author should meet all of these four conditions. After the initial submission of a manuscript, any changes whatsoever in authorship (adding author(s), deleting author(s), or re-arranging the order of authors) must be explained by a letter to the editor from the authors concerned. This letter must be signed by all authors of the paper. Copyright assignment must also be completed by every author.

- Corresponding author and first author: JYMS does not allow multiple corresponding authors for one article. Only one author should correspond with the editorial office and readers for one article. JYMS does accept notice of equal contribution for the first author when the study was clearly performed by co-first authors.
- Correction of authorship after publication: JYMS does not correct authorship after publication unless a mistake has been made by the editorial staff. Authorship may be changed before publication but after submission when an authorship correction is requested by all of the authors involved with the manuscript.

Originality, plagiarism and duplicate publication

Submitted manuscripts must not have been previously published or be under consideration for publication elsewhere. No part of the accepted manuscript should be duplicated in any other scientific journal without the permission of the Editorial Board. Submitted manuscripts are screened for possible plagiarism or duplicate publication by Similarity Check using 'Turnitin' program (iParadigms, LLC., Oakland, CA, USA) upon arrival. If plagiarism or duplicate publication is detected, the manuscripts may be rejected, the authors will be announced in the journal, and their institu-

tions will be informed. There will also be penalties for the authors.

A letter of permission is required for any and all material that has been published previously. It is the responsibility of the author to request permission from the publisher for any material that is being reproduced. This requirement applies to text, figures, and tables.

Secondary publication

It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by International Committee of Medical Journal Editors (ICMJE), available from http://www.icmje.org. These are:

- The authors have received approval from the editors of both journals (the editor concerned with the secondary publication must have access to the primary version).
- The priority for the primary publication is respected by a publication interval negotiated by editors of both journals and the authors.
- The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
- The secondary version faithfully reflects the data and interpretations of the primary version.
- The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first reported in the (journal title, with full reference)"—and the secondary version cites the primary reference.
- The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the United States National Library of Medicine (NLM) does not consider translations as "republications" and does not cite or index them when the original article was published in a journal that is indexed in MEDLINE.

Registration of the clinical trial research

Clinical trial defined as “any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome” should be registered to the primary registry to be prior publication. JYMS accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/en/), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), ISRCTN Resister (www.ISRCTN.org), or the Clinical Research Information Service (CRIS), Korea CDC (https://cris.nih.go.kr/cris/index.jsp). The clinical trial registration number shall be published at the end of the abstract.

Data sharing statement

JYMS accepts the ICMJE Recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf). All manuscripts reporting clinical trial results should submit a data sharing statement following the ICMJE guidelines from 1 July 2018. Authors may refer to the editorial, “Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors,” in JKMS Vol. 32, No. 7:1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

Process to manage the research and publication misconduct

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author’s idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of JYMS will discuss the suspected cases and reach a decision. JYMS will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

For the policies on research and publication ethics not stated in the Instructions, Guidelines on Good Publication (http://publicationethics.org) or Good Publication Practice Guidelines for Medical Journals (http://kamje.or.kr) can be applied.

Research and publication ethics form

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Affiliation: _____

Author's name (please print): _____

Manuscript title: _____

All authors pledges that we follow the basic standards of research and publication ethics in the submission process to *Journal of Yeungnam Medical Science*

Check Yes if Research subject, research object and size, setting of controls, and the methods of data collection are suitable for the research ethics.	☐ ***Yes*** ☐***No***
Check Yes if Authors should ensure that their submitted manuscripts are not against publication ethics such as fabrication, falsification or plagiarism.	☐ ***Yes*** ☐***No***
Check Yes if In clinical research involving human, informed consent from patient should be conducted and written in the method section of the manuscript.	☐ ***Yes*** ☐***No***
Check Yes if All clinical research involving human and animal subjects to be approved by the author's Institutional Review Board (IRB) or equivalent committees.	☐ ***Yes*** ☐***No***
Check Yes if This study is conducted in compliance with the Declaration of Helsinki and this comment is written in the method section of the manuscript.	☐ ***Yes*** ☐***No***
Check Yes if All Authors must disclose all relationships that could be viewed as potential conflicts of interest. This relationship also includes any potential conflicts of interest with all material, products, and companies in the manuscript.	☐ ***Yes*** ☐***No***
Check Yes if Authors should confirm that the submitted work is not under consideration or accepted for publications elsewhere, and would not be submitted in any other journals after acceptance.	☐ ***Yes*** ☐***No***
Check Yes if Duplicate publication, which includes 'imalas publication', 'plagiarism', and 'salami publication', is strictly not conducted.	☐ ***Yes*** ☐***No***

If the rationale provided by the authors remains unsatisfactory in the judgment of the editors, the manuscript will be rejected or retracted. The authors will not be allowed to subsequently submit their research to *Journal of Yeungnam Medical Science*. The authors should keep the above mentioned disadvantages in mind.

Date: _____

Corresponding author's name: _____

Copyright transfer agreement

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

The author(s) submit manuscript with the following title

_____

_____

In consideration of editors and publisher's effort in reviewing and editing our/my Article, the undersigned authors hereby transfer, convey, and assign all copyrights in the Article to the Editorial Board of the *Journal of Yeungnam Medical Science*. The copyright transfer covers the right to print, publish, distribute and sell throughout the world the said contribution and parts thereof, including all revisions or versions and future editions, in all forms and media.

The authors certify that I have participated in the intellectual content, the analysis of data, and the writing of the Article, to take public responsibility for it The authors reviewed the final version of the Article, believe it represents valid work and approve it for publication The authors certify that none of the material in the manuscript has been published previously, is included in another manuscript The authors also certify that the Article has not been accepted for publication elsewhere, nor have they assigned any right or interest in the Article to any third party. The authors will obtain and include with the manuscript written permission from any respective copyright owners for the use of any text, figures, and tables that have been previously published. The authors agree that it is their responsibility to pay fees charged for permissions.

Author's name	**Signature**
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Patient photographic and videographic consent, authorization and release form

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

I am informed and aware of photographs, videotapes and other images (imaging records) taken by Dr. _____ or his designee(s) of myself or any parts of my body regarding surgical procedures carried out by Dr. _____ . I understand and consent that such imaging records may and will be used by Dr. _____ as reference in diagnosing and treating other patients in the future. I further consent to the release and transfer of copyright ownership by Dr. to *Journal of Yeungnam Medical Science* of such imaging records.

I understand that by consenting on release of my imaging records, these may and will be used in upcoming issue or issues of the journal, as well as on the journal website, or any other print or electronic media for the purpose of informing medical professionals or other readers about surgical methods. I understand that when these imaging records are included in any articles, medical information regarding sex, age, operative date and treatment results may and will be included together. But I, nor any member of my family, will be identied by name in any publication, and any information that may aid in identifying me or my family will not be exposed. (In case of facial photographs, the photo is cropped to only necessary parts in order to make individual identication impossible.) I understand that whether I consent on this form or not, it bears no consequences whatsoever on any future actions, and that there will be no eect on the medical treatment I receive from Dr. _____ or any subordinates.

I grant this consent as a voluntary contribution in the interest of public education, and certify that I have read the above Consent, Authorization and Release form and fully understand its terms. I understand that, if I do not revoke this authorization, it will expire ten years from the date written below.

I hereby transfer in above-mentioned terms, the copyright of my imaging records to

Dr. _____ .

20 . . .

Name: _____ **Signature:** _____

Hospital: _____ **Department:** _____

Designated Doctor: _____ **Signature:** _____