Aims and scope

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“Another color of the world”

Laugavegur trail in Iceland

*Photograph by In Hwan Song, 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
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 beta-histine, 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 neuritis. The clinical features of vestibular neuritis were first reported by Eric Ruttin in 1909 and later by Carl-Olof Nylen in 1924 [7,8]. The term “vestibular neuritis” was first described by Charles Skinner Hallpike in 1949 and Margaret Ruth Dix and Charles Skinner Hallpike in 1952 [9]. Vestibular neuritis 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.
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 nerve 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/or infarction [16,18].

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

**Notes**

**Conflicts of interest**

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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...
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>
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<tr>
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<td></td>
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</tr>
<tr>
<td></td>
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</tr>
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<td></td>
<td>Allows selection of specific antigens to be combined for a multivalent vaccine</td>
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</tr>
<tr>
<td></td>
<td>Highly adaptable</td>
<td></td>
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</tbody>
</table>

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 adeno viral 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 Ad-CLD-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-skewed 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.

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**Author contributions**

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

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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
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.

<table>
<thead>
<tr>
<th>Generation of private and public keys using the Elliptic Curve Digital Signature Algorithm</th>
</tr>
</thead>
</table>

```java
// 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);
}
```

(Continued to the next page)
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-----
MGwCAQAwEAYHCoZIzj0CAQYFK4EAAAEVTBTAgEBBBUCoeEILPfBmQlV3CRHiHo+S3++ka8egBwYFK4EEAAAGhMsAAAQGyQ46vQ9dGw-tab7xZtjFdcGu0fHQR+ZOnNX8k/xYjkrRjGTBEU=
-----END EC PRIVATE KEY-----

-----BEGIN EC PUBLIC KEY-----
MEAwEAYHCoZIzj0CAQYFK4EAAEDLAEEArqROOr0PXRusLWm+8WbSTBXXCBrtHs0EfmrTpzV/JP8W5K0YxkwRF
-----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-
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(privateKey);
    // A function to extract the public key from the certificate of a text string format:
    this.publicKey = new EC().readPublicKeyFromPemFile(publicKey);
}

// The validity of the key is verified.
public static boolean isKeyVerify(String id, PrivateKey privateKey, 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.getPatientsData());

// The transaction information to be propagated is created.
// The transaction information includes the patient’s medical information, key information, electronically signed data, and transaction generation time.
public Transaction(Key key, String patientsData) throws Exception {
    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)
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.length; i++) {
      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**

<table>
<thead>
<tr>
<th>Block number</th>
<th>Created time</th>
<th>Previous hash</th>
<th>Block hash</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2021-06-14 01:51:36.640</td>
<td>null</td>
<td>74234e98afe7498fb5daf1f36ac2d78acc339464f-950703b8c019892f982b90b</td>
</tr>
<tr>
<td>1</td>
<td>2021-06-14 01:51:39.661</td>
<td>74234e98afe7498fb5daf1f36ac2d78acc339464f-950703b8c019892f982b90b</td>
<td>6345e8d4fe0b749dfe1862cbfd90817f38dd3692cd2cd918be5e5becd540944</td>
</tr>
<tr>
<td>2</td>
<td>2021-06-14 01:51:42.704</td>
<td>6345e8d4fe0b749dfe1862cbfd90817f38dd3692cd2cd918be5e5becd540944</td>
<td>dbf72d6bf7143b6272308fb0708291c0733c078553535753fb90e477113a7e</td>
</tr>
</tbody>
</table>

**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 the next page)
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: dbf72d6bf7143b6272308fb0708291c10733c0f78753355753fb90e477113a7e
Block hash: f55e598438047feefac137016eda9533962444e148730499727203e72733
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 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

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.

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

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References


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

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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 included 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
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/Mobilius 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 (aSi1000) 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 cm² 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

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

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

https://doi.org/10.12701/yujm.2021.01123
Fig. 1. Patient-specific quality assurance with amorphous silicon (aSi1000) 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.
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 be-
tween 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 de-
ivered by the log files, and Fig. 4C shows the gamma (0.6%/0.6
mm) evaluation between the planned and delivered fluence imag-
es.

FractionLab performs gamma evaluation between the automati-
cally calculated 2D fluence and the 2D fluence generated using the
log files after irradiation. The machine log files include the deliv-
ered MLC position information as a function of the fractional
dose, which is used by FractionLab to create fluence maps magni-
fied 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. Fraction-
Lab 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 an-
gle 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 evalua-
tion. 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-
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.

**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-

**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**

<table>
<thead>
<tr>
<th>Gamma criteria (%)/mm</th>
<th>Gamma passing ratesa</th>
<th>Gamma passing ratesb</th>
<th>Gamma passing rate (3%/3 mm)</th>
<th>p-valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1/0.1</td>
<td>69.7 (37.7–77.3)</td>
<td>98.1 (95.5–100)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>0.2/0.2</td>
<td>70.6 (40.1–77.6)</td>
<td>98.1 (95.5–100)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>0.3/0.3</td>
<td>72.4 (48.3–86.3)</td>
<td>98.1 (95.5–100)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>0.4/0.4</td>
<td>74.5 (54.5–94.4)</td>
<td>98.1 (95.5–100)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>0.5/0.5</td>
<td>96.4 (90.4–99.6)</td>
<td>98.1 (95.5–100)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>0.6/0.6</td>
<td>97.5 (92.3–99.7)</td>
<td>98.1 (95.5–100)</td>
<td>0.127</td>
<td></td>
</tr>
<tr>
<td>0.7/0.7</td>
<td>97.8 (92.5–99.9)</td>
<td>98.1 (95.5–100)</td>
<td>0.519</td>
<td></td>
</tr>
<tr>
<td>0.8/0.8</td>
<td>98.1 (92.8–99.9)</td>
<td>98.1 (95.5–100)</td>
<td>0.965</td>
<td></td>
</tr>
<tr>
<td>0.9/0.9</td>
<td>98.5 (93.0–100.0)</td>
<td>98.1 (95.5–100)</td>
<td>0.306</td>
<td></td>
</tr>
<tr>
<td>1.0/1.0</td>
<td>99.5 (98.1–100.0)</td>
<td>98.1 (95.5–100)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

aMedian (range). bBy paired t-test.

FractionLab, Varian/Mobius Medical System, Houston, TX, USA.

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.
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 accelerators (VitalBeam, Trilogy, Clinac 21EXS, and Clinac 1x [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.

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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.

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16. Han B, Ding A, Lu M, Xing L. Pixel response-based EPID do-


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.
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

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**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).
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.

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.

Table 3. Demographic of participants

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

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

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

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

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

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

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.

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**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.

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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

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


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

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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 gemcitabine.
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, FOLFIRINOX 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

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

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.

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

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

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.
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 chemotherapy.

---

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

<table>
<thead>
<tr>
<th>The second-line regimen</th>
<th>First-line regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gemcitabine (± erlotinib)</td>
</tr>
<tr>
<td>Gemcitabine (± erlotinib)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gemcitabine+nab-paclitaxel</td>
<td>7 (18.4)</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>12 (31.6)</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>8 (21.1)</td>
</tr>
<tr>
<td>5-FU+cisplatin</td>
<td>6 (15.8)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (13.2)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (100)</td>
</tr>
</tbody>
</table>

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, 5-1 (one patient each).

---

![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.](https://doi.org/10.12701/yujm.2021.01347)
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 the second-line treatment were statistically significant (Table 4). In the univariate analysis of OS, poor ECOG PS (≥ 2), metastatic disease, liver metastasis, bone metastasis, and elevated serum carcinoembryonic antigen (CEA) level 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).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median PFS (mo)</th>
<th>Univariate analysis</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>( \rho )-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>EGOG PS(^a)</td>
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<td></td>
</tr>
<tr>
<td>0–1</td>
<td>4.5</td>
<td>1.070 (0.426–2.684)</td>
<td>0.886</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>6.0</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3.4</td>
<td>0.577 (0.345–0.965)</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6.8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Disease extent(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>9.8</td>
<td>3.082 (1.588–5.984)</td>
<td>0.001</td>
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<tr>
<td>Metastatic</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver metastasis(^c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6.1</td>
<td>1.811 (1.103–2.976)</td>
<td>0.017</td>
<td></td>
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<tr>
<td>Yes</td>
<td>3.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung metastasis(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4.9</td>
<td>1.797 (1.005–3.215)</td>
<td>0.045</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone metastasis(^e)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5.4</td>
<td>5.512 (2.094–12.677)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA19-9 (U/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 221</td>
<td>5.7</td>
<td>1.016 (0.618–1.670)</td>
<td>0.951</td>
<td></td>
</tr>
<tr>
<td>≥ 221</td>
<td>3.7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CEA(^f) (ng/mL)</td>
<td></td>
<td></td>
<td></td>
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<tr>
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</table>

PFS, progression-free survival; HR, hazard ratio; CI, confidence 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.

\(^b\) p < 0.05.

### 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.
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

<table>
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<tr>
<th>Variable</th>
<th>Median OS (mo)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
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<td>HR (95% CI)</td>
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<td>CA19-9 (U/mL)</td>
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<td>1.939 (1.065–3.530)</td>
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</table>

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.

*At start of second-line chemotherapy.

\( p < 0.05 \).
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.

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

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References

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].
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. 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.
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>
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<th>Characteristic</th>
<th>Overall</th>
<th>Survivor</th>
<th>Non-surgeon</th>
<th>p-value</th>
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<td>25 (55.6)</td>
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<td>93 (52)</td>
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<td>35 (15.6)</td>
<td>33 (18.4)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Stoma only</td>
<td>11 (4.9)</td>
<td>10 (5.6)</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Drainage only</td>
<td>4 (1.8)</td>
<td>2 (1.1)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Stoma creation</td>
<td>120 (53.6)</td>
<td>88 (49.2)</td>
<td>32 (71.1)</td>
<td>0.013</td>
</tr>
<tr>
<td>No stoma creation</td>
<td>104 (46.4)</td>
<td>91 (50.8)</td>
<td>13 (28.9)</td>
<td></td>
</tr>
<tr>
<td>Causes of perforation</td>
<td></td>
<td></td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td>Malignancy</td>
<td>54 (24.1)</td>
<td>41 (22.9)</td>
<td>13 (28.9)</td>
<td></td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>37 (16.5)</td>
<td>30 (16.8)</td>
<td>7 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>41 (18.3)</td>
<td>39 (21.8)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Ischemic colitis</td>
<td>16 (7.1)</td>
<td>9 (5.0)</td>
<td>7 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Stercoral</td>
<td>39 (17.4)</td>
<td>28 (15.6)</td>
<td>11 (24.4)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>24 (10.7)</td>
<td>21 (11.7)</td>
<td>3 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (5.8)</td>
<td>11 (6.1)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number only, number (%), or mean ± standard deviation.
ASA, American Society of Anesthesiologists; PS, physical status.
Table 2. Comparison of perioperative factors between the survivors and non-survivors

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

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivor (n = 179)</th>
<th>Non-survivor (n = 45)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal surgeon</td>
<td>137 (76.5)</td>
<td>30 (66.7)</td>
<td>0.243</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>169.5 ± 67.1</td>
<td>186.2 ± 131.1</td>
<td>0.235</td>
</tr>
<tr>
<td>Intraoperative lavage</td>
<td>14 (7.8)</td>
<td>2 (4.4)</td>
<td>0.745</td>
</tr>
<tr>
<td>Stoma reversal</td>
<td>64 (72.7)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>47 (26.3)</td>
<td>10 (22.2)</td>
<td>0.716</td>
</tr>
<tr>
<td>Intraabdominal abscess</td>
<td>36 (20.1)</td>
<td>8 (17.8)</td>
<td>0.887</td>
</tr>
<tr>
<td>Septic shock</td>
<td>9 (5.0)</td>
<td>40 (88.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>19 (10.6)</td>
<td>8 (17.8)</td>
<td>0.288</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>3 (1.7)</td>
<td>13 (28.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paralytic ileus</td>
<td>8 (4.5)</td>
<td>0 (0)</td>
<td>0.363</td>
</tr>
<tr>
<td>Anastomosis leakage</td>
<td>2 (1.1)</td>
<td>6 (13.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>1 (0.6)</td>
<td>39 (86.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

NA, not applicable.

*The stoma reversal rate was based on 88 survivors among patients with stoma creation.
Table 4. Analysis of mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 70</td>
<td>3.496 (1.667–7.331)</td>
<td>0.001</td>
</tr>
<tr>
<td>Comorbidity, ≥ 2</td>
<td>3.032 (1.549–5.934)</td>
<td>0.001</td>
</tr>
<tr>
<td>Organ failure</td>
<td>4.702 (2.353–9.397)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3.568 (1.663–7.658)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prolonged prothrombin time (&gt; 15 sec)</td>
<td>3.225 (1.646–6.319)</td>
<td>0.001</td>
</tr>
<tr>
<td>Free fluid</td>
<td>3.225 (1.497–6.947)</td>
<td>0.003</td>
</tr>
<tr>
<td>Feculent fluid</td>
<td>2.222 (1.144–4.317)</td>
<td>0.018</td>
</tr>
<tr>
<td>Diffuse peritonitis</td>
<td>4.173 (1.838–9.472)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sidedness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right location</td>
<td>2.244 (1.125–4.477)</td>
<td>0.022</td>
</tr>
<tr>
<td>Left location</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval.

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

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

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

^aStatistical significance was assessed by Fisher exact test.

Lee et al. Colonic perforation surgery: patient outcome and prognostic factors

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.

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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.

References

11. Richards CH, Roxburgh CS; Scottish Surgical Research Group (SSRG). Surgical outcome in patients undergoing reversal of...


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

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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

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*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 FOLF-OX (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/m² twice a day, day [D] 1–D14) and CAPOX therapy (oxaliplatin of 130 mg/m², D1 and capecitabine of 1,000 mg/m² 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/m², D1; leucovorin of 400 mg/m², D1; 5-FU of 400 mg/m² bolus, D1; and 5-FU of 2,400 mg/m² 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/m² and leucovorin of 20 mg/m², 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...
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 mqr-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 (DSS346, BAT26, BST25, D17S250, and D2S123). The amplified PCR products were analyzed using a Model 3500 x 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**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>MMR status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MSI-H/dMMR</td>
</tr>
<tr>
<td>No. of patients</td>
<td>286 (100)</td>
<td>54 (18.9)</td>
</tr>
<tr>
<td>Age</td>
<td>70 (25–88)</td>
<td>71 (40–86)</td>
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<td>Sex</td>
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<td>Male</td>
<td>153 (53.5)</td>
<td>133 (46.5)</td>
</tr>
<tr>
<td>Female</td>
<td>133 (46.5)</td>
<td>30 (22.6)</td>
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<tr>
<td>Primary tumor location</td>
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<tr>
<td>Ascending colon</td>
<td>100 (35.0)</td>
<td>30 (30.0)</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>56 (19.6)</td>
<td>13 (23.2)</td>
</tr>
<tr>
<td>Descending colon</td>
<td>130 (45.5)</td>
<td>11 (8.5)</td>
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<tr>
<td>Right</td>
<td>147 (51.4)</td>
<td>41 (27.9)</td>
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<tr>
<td>Left</td>
<td>139 (48.6)</td>
<td>13 (9.4)</td>
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<td>T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>51 (17.8)</td>
<td>7 (13.7)</td>
</tr>
<tr>
<td>T3</td>
<td>235 (82.2)</td>
<td>47 (20.0)</td>
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<tr>
<td>No. of sampled LNs</td>
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<td></td>
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<tr>
<td>&lt; 12</td>
<td>28 (9.8)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>≥ 12</td>
<td>258 (90.2)</td>
<td>51 (19.8)</td>
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<td>5 (22.7)</td>
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<td>49 (18.6)</td>
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<tr>
<td>Perforation</td>
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<td>283 (99.0)</td>
<td>54 (19.1)</td>
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<td>25 (8.7)</td>
<td>11 (44.0)</td>
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<tr>
<td>No</td>
<td>261 (91.3)</td>
<td>43 (16.5)</td>
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<td>Perineural invasion</td>
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<td>162 (56.6)</td>
<td>31 (19.1)</td>
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<td>124 (43.4)</td>
<td>23 (18.5)</td>
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<td>Lymphovascular invasion</td>
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<td>Yes</td>
<td>184 (64.3)</td>
<td>35 (19.0)</td>
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<td>No</td>
<td>102 (35.7)</td>
<td>19 (18.6)</td>
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<td>ESMO guidelines</td>
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<tr>
<td>Intermediate risk</td>
<td>115 (40.2)</td>
<td>29 (25.2)</td>
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<td>High risk</td>
<td>171 (59.8)</td>
<td>25 (14.6)</td>
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<td>Adjuvant chemotherapy</td>
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<td>Yes</td>
<td>201 (70.3)</td>
<td>37 (18.4)</td>
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<td>No</td>
<td>85 (29.7)</td>
<td>17 (20.0)</td>
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<tr>
<td>Oxaliplatin-contained</td>
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<tr>
<td>Yes</td>
<td>98 (48.8)</td>
<td>21 (21.4)</td>
</tr>
<tr>
<td>No</td>
<td>103 (51.2)</td>
<td>16 (15.5)</td>
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<td>Relapse</td>
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<tr>
<td>Yes</td>
<td>32 (11.2)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>No</td>
<td>254 (88.8)</td>
<td>52 (20.5)</td>
</tr>
<tr>
<td>Death</td>
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<td></td>
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<td>Yes</td>
<td>19 (6.6)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>No</td>
<td>267 (93.4)</td>
<td>53 (19.9)</td>
</tr>
</tbody>
</table>

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.
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 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 patient 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 patient 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.](https://doi.org/10.12701/yujm.2021.01571)
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 \[23\].
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].

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

<table>
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<tr>
<th>Variable</th>
<th>Disease-free survival</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Univariate analysis</td>
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<td>Multivariate analysis</td>
<td></td>
<td></td>
<td>p-value</td>
<td></td>
<td>p-value</td>
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<tr>
<td></td>
<td>HR (95% CI)</td>
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<td>HR (95% CI)</td>
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<td>p-value</td>
<td></td>
<td>p-value</td>
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</tr>
<tr>
<td>Age, ≥ 65 yr</td>
<td>3.782 (1.325–10.794)</td>
<td>0.013</td>
<td></td>
<td>2.335 (0.795–6.857)</td>
<td>0.123</td>
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<tr>
<td>Male sex</td>
<td>1.120 (0.559–2.262)</td>
<td>0.741</td>
<td></td>
<td>1.016 (0.481–2.146)</td>
<td>0.967</td>
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<tr>
<td>Primary tumor sidedness, right</td>
<td>1.425 (0.708–2.865)</td>
<td>0.321</td>
<td></td>
<td>1.558 (0.727–3.339)</td>
<td>0.255</td>
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<tr>
<td>Tumor stage, T4</td>
<td>4.027 (2.002–8.098)</td>
<td>&lt; 0.001</td>
<td></td>
<td>4.679 (2.020–10.838)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Sampled LNs, &lt; 12</td>
<td>1.715 (0.697–4.219)</td>
<td>0.240</td>
<td></td>
<td>2.053 (0.745–5.658)</td>
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<tr>
<td>Obstruction, yes</td>
<td>2.268 (0.309–16.667)</td>
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<tr>
<td>Perforation, yes</td>
<td>20.366 (0.000–6.956×10⁰)</td>
<td>0.764</td>
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<tr>
<td>High-grade tumor, yes</td>
<td>22.896 (0.087–6.050×10⁲)</td>
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<tr>
<td>Perineural invasion, yes</td>
<td>1.040 (0.516–2.098)</td>
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<tr>
<td>Lymphovascular invasion, yes</td>
<td>2.644 (1.284–5.448)</td>
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<td>1.393 (0.625–3.106)</td>
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<tr>
<td>Adjuvant chemotherapy, no</td>
<td>3.592 (1.783–7.240)</td>
<td>&lt; 0.001</td>
<td></td>
<td>3.967 (1.910–8.239)</td>
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<tr>
<td>Oxaliplatin-contained, no</td>
<td>2.720 (0.866–8.544)</td>
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<td>MMR status, low/MSS</td>
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</table>

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

Table 3. Univariate and multivariate analyses for overall survival

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<tr>
<th>Variable</th>
<th>Overall survival</th>
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<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
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<td>Multivariate analysis</td>
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<td>p-value</td>
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<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
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</tr>
<tr>
<td>Age, ≥ 65 yr</td>
<td>4.629 (1.068–20.058)</td>
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<td>2.727 (0.604–12.301)</td>
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<tr>
<td>Male sex</td>
<td>1.645 (0.657–4.202)</td>
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<td></td>
<td>1.645 (0.598–4.525)</td>
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</tr>
<tr>
<td>Primary tumor sidedness, right</td>
<td>1.166 (0.472–2.879)</td>
<td>0.739</td>
<td></td>
<td>1.301 (0.477–3.548)</td>
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<tr>
<td>Tumor stage, T4</td>
<td>5.324 (2.104–13.466)</td>
<td>&lt; 0.001</td>
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<td>7.568 (2.313–24.766)</td>
<td>0.001</td>
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<tr>
<td>Sampled LNs, &lt; 12</td>
<td>1.076 (0.304–3.817)</td>
<td>0.909</td>
<td></td>
<td>1.866 (0.446–7.813)</td>
<td>0.393</td>
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<tr>
<td>Obstruction, yes</td>
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</tr>
<tr>
<td>Perforation, yes</td>
<td>20.336 (0.000–4.319×10⁵)</td>
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<tr>
<td>High-grade tumor, yes</td>
<td>22.724 (0.011–4.899×10⁶)</td>
<td>0.425</td>
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<tr>
<td>Perineural invasion, yes</td>
<td>2.075 (0.770–5.595)</td>
<td>0.149</td>
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<tr>
<td>Lymphovascular invasion, yes</td>
<td>2.172 (0.831–5.675)</td>
<td>0.114</td>
<td></td>
<td>1.116 (0.378–3.296)</td>
<td>0.843</td>
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<td>Adjuvant chemotherapy, no</td>
<td>3.344 (1.311–8.534)</td>
<td>0.012</td>
<td></td>
<td>4.525 (1.627–12.579)</td>
<td>0.004</td>
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<tr>
<td>Oxaliplatin-contained, no</td>
<td>1.957 (0.489–7.839)</td>
<td>0.343</td>
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<tr>
<td>MMR status, low/MSS</td>
<td>0.453 (0.591–33.561)</td>
<td>0.147</td>
<td></td>
<td>2.812 (0.350–22.560)</td>
<td>0.331</td>
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HR, hazard ratio; CI, confidence interval; LN, lymph node; MMR, mismatch repair; MSS, microsatellite stable.
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.

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References


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

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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; Feto-fetal 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.
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.

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None.

**Author contributions**

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

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**References**

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
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, <15 IU/mL), anti-ribonuclear protein antibody (Ab) of 0.53 U/mL ( < 15 IU/mL), anti-smith Ab of 0.3 U/mL ( < 10 U/mL), and anti-Smith Ab of 0.3 U/mL ( < 10 U/mL). The patient was 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 polynuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. Based on germinal center regression and plasmacytosis with histopathologic features of enlarged lymph nodes at
≥ 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. 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.
Contrary 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-

Fig. 2. (A-C) Diffusely enhanced 18F-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).
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 mono-
therapy, an IL-6 inhibitor, siltuximab (11 mg/kg, every 3 weeks),
was administered while tapering prednisolone. On continuing si-
tuximab 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 attenua-
tions 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. Af-
ter treatment for more than 30 months, the patient has maintained
a favorable partial response to siltuximab without further progres-
sion 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 dis-

tinct 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 dis-
ease. 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, poly-

clonal lymphoproliferation, and life-threatening multiple organ
dysfunction [6,9] due to IL-6 overproduction from activated plas-
ma cells [10]. MCD is most commonly associated with HHV-8 or
HHV. HHV-8 or the HHV-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 dis-
orders, 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 consist-
tent with pulmonary LCH. LCH is characterized by aberrant func-
tion and proliferation of cells of the mononuclear phagocyte sys-
tem and infiltration of organs by Langerhans cells [11]. Typical
pathologic findings of LCH are heterogeneous collections of Lang-
erhans cells with eosinophils, neutrophils, small lymphocytes, and
histiocytes that might form multinucleated giant cells. Occasion-
ally, eosinophilic abscesses might be present, demonstrating central
necrosis and positive S-100 protein, CD1a, and HLA-DR in im-
munohistochemical stains [11]. However, in the present case, lung
biopsy showed no presence of Langerhans cells and negative stain-
ing for S-100 protein. Bone marrow aspiration and biopsy revealed
hypercellular marrow (cellularity of 80%) with an increase in plas-
ma cells (11.0%). There was no evidence of Langerhans cell dis-
ease on lymph node biopsy.

An excisional biopsy of the lymph node showed interfollicular
marked plasmacytosis, regressed germinal centers with IgG4 posi-
tivity 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 immunohisto-
chemical staining of HHV8 and S-100 protein. However, IgG and
IgG4 positive cells were as many as 400/HPF and 100/HPF, re-
spectively.

IgG4-RD is pathologically characterized by diffuse lymphoplas-
mytic 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 associa-
tion with histopathological features for the final diagnosis. Mo-
chizuki 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 hypercholesterolemia, 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 m²), (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, atilizumab) 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.

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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.

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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.
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.
**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.
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...
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
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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
Palisaded encapsulated neuroma on the lower lip: a case report

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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 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

Case

Ethical statements: 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.
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 neumomas 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

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

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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.
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). Tropinin-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 caretaker 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. Tropinin-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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sudden change to LBBB</th>
<th>Convert to NSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated LVEF</td>
<td>36%</td>
<td>44%</td>
</tr>
<tr>
<td>Left ventricular RWMA</td>
<td>Basal and mid segments - severe hypokinetic</td>
<td>Basal segment - mild hypokinetic</td>
</tr>
<tr>
<td>Valvular state (stenosis/regurgitation)</td>
<td>Non-specific</td>
<td>Non-specific</td>
</tr>
</tbody>
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LBBB, left bundle branch block; NSR, normal sinus rhythm; LVEF, left ventricular ejection fraction; RWMA, regional wall motion abnormality.
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 drain-
age. 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 dys-function.

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 exhibit-
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

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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. (In case of facial photographs, the photo is cropped to only necessary parts in order to make individual identification 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 effect 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: ____________________________