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The old biomarkers you know are still useful: D-dimer and troponin I

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See "Troponin I and D-dimer levels as triaging biomarkers to distinguish acute pulmonary thromboembolism from myocardial infarction" by Soo-Jin Kim, Moo Hyun Kim, Kwang Min Lee, Jin Woo Lee, Young Shin Cha, Da Eun Koh, Joo Yeong Hwang, Jong Sung Park

Acute chest pain and dyspnea remain challenging presentations to diagnose and differentiate in emergency settings. These symptoms can occur in a variety of critical conditions, including acute coronary syndrome, which encompasses non-ST segment elevation myocardial infarction (NSTEMI), as well as acute aortic syndrome (AAS), acute pulmonary thromboembolism (APTE), tension pneumothorax, and esophageal rupture. Although distinguishing between APTE and NSTEMI can be difficult, it is important to identify these conditions promptly and treat them effectively to reduce mortality and improve patient outcomes. D-Dimer (DD), a degradation product of cross-linked fibrin, is widely recognized for its diagnostic value in APTE due to its high negative predictive value. However, DD is not specific and may be elevated in various conditions, including myocardial infarction, infection, cancer, trauma, and other inflammatory diseases [1]. Cardiac troponin I (CTI), a biomarker specific to cardiac tissue, is highly useful for diagnosing myocardial infarction. It can also be elevated in cases of APTE, which may cause right ventricular dysfunction and myocardial damage [1-3]. Several studies have been conducted to differentiate between APTE and NSTEMI using biomarkers such as DD and CTI [4-6]. Kim et al. [6] demonstrated that DD and CTI are useful in differentiating APTE from NSTEMI. Their study proposed a decision tree model for the differential diagnosis of APTE, based on initial DD levels of 3.18 μg/mL and initial CTI levels of 1.14 ng/mL.

In this issue of *Kosin Medical Journal*, Kim et al. [7] validated the tree model algorithm on an additional dataset by comparing it to a test set including the subjects of a prior study [6]. The estimated accuracy rates for the two sets were notably similar (test set: 91%, validation set: 88.6%). Moreover, Kim et al. [7] introduced a decision-making tree for the rapid diagnosis of APTE or NSTEMI, utilizing an initial DD level of 1.5 μg/mL and an initial CTI level of 0.1 ng/mL. A previous study also indicated that a ratio of DD to CTI with a cutoff value of 1.82 could be clinically useful for distinguishing APTE from NSTEMI [5]. These findings suggest that using both DD and CTI levels is more effective than

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using either marker alone to differentiate between APTE and NSTEMI. The algorithm proposed by Kim et al., or a metric such as the ratio of DD to CTI, appears to be beneficial for quickly determining the next steps, such as whether to perform chest computed tomography or coronary angiography, and for reducing unnecessary coronary angiography. A prior study reported an 11.1% rate of unnecessary coronary angiography in cases of APTE (10/90), which was linked to bleeding complications following thrombolysis [5]. Therefore, in the emergency setting, this decision-making tree for patients with acute chest pain or dyspnea may prevent unnecessary invasive procedures and improve the clinical outcomes of APTE.

Another recent study showed that the ratio of DD to CTI, with a cutoff value of 81.3, may also be useful for differentiating thoracic AAS from NSTEMI [8]. This value of the ratio of DD to CTI was notably higher than that reported in a previous study [5], although the conditions being compared were different (differentiating APTE from NSTEMI or AAS from NSTEMI). An explanation for this discrepancy is that the recent (or latest) study [8] utilized high-sensitivity troponin T (ng/mL) measurements instead of conventional troponin I. Based on these findings, it is advisable to consider not only the troponin unit but also the type of troponin–whether conventional troponin I or high-sensitivity troponin I–when applying these research findings in clinical practice.

Although this study [7] had several limitations, such as its retrospective nature, being a single-center study, and not accounting for the time interval between symptom onset and emergency room visit–which is significant because DD and CTI levels can change over time–the tree model algorithm and the decision-making tree for the rapid diagnosis of APTE or NSTEMI could be beneficial. These tools offer a rapid and straightforward method to reduce misdiagnoses and unnecessary invasive procedures, potentially improving clinical outcomes for patients presenting with acute chest pain and dyspnea by rapidly assessing DD and CTI levels in the emergency setting. Further large-scale prospective studies are required to validate their effectiveness in real-world clinical practice.

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Review article

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Prevention of myopia progression using orthokeratology

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The prevalence of myopia in children and juveniles has increased significantly in Korea and worldwide; in particular, the rates of myopia and high myopia in East Asia have grown rapidly. Myopia is easily corrected with spectacles or contact lenses. However, as children grow and mature, myopia can progress irreversibly and lead to vision-threatening complications. Thus, the prevention of myopia progression is an essential treatment goal. Many treatment strategies are being employed, including atropine eyedrops, specialized glasses, and orthokeratology (Ortho-K) lenses. Ortho-K is an effective treatment in managing myopia progression by lowering the rate of increase in refractive error and axial length. In this article, we review Ortho-K as a treatment for myopia progression, its history, mechanism, treatment regimen, and safety profile.

Keywords: Atropine; Axial length, eye; Contact lenses; Eyeglasses; Myopia

Introduction

Myopia, more commonly known as nearsightedness, is a condition in which the image of a distant object is formed in front of the retina due to a mismatch between the optical refractive power of the eye and the axial length. Myopia is derived from the Greek *myōps* (myein, to close + ōps, the eye) meaning "short-sighted." This concept dates back to B.C. 350 where a link between myopia, bulging eyes, frequent blinking, eyelid squeezing, close reading were theorized [1,2]. Now, after two millennia, myopia is one of the most common eye conditions worldwide. This increased prevalence has led to increased interest and awareness of myopia progression and the risk of sight-threatening complications. To mitigate the risk of these complications, many strategies to delay the progression of myopia are being used and investigated. Through this review based on traditional methods [3], we focused on the role of orthokeratology (Ortho-K) in decreasing the progression of myopia.

Epidemiology of myopia

Myopia is prevalent worldwide but has a strikingly higher prevalence in East Asia [4]. The prevalence in schoolchildren were reported at 80.2% in Korea [5], 80.7% in China [6], 76.67% in Taiwan [4], and 74.2% in Singapore [7]. In addition, an increased prevalence was also found in children of Asian descent living elsewhere [8]. With these numbers projected to rise in the coming decades, myopia is considered a global epidemic and an imminent public health concern. The estimated worldwide prevalence of myopia was 22.9% of the world population [9]. It is projected that by 2050, 49.8% of the population will be myopic, with 9.8% having high myopia of more than 5.00 D [9]. Traditionally, vision is

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improved in myopes by glasses, contact lenses, or refractive surgery. However, progression to high and pathologic myopia can lead to an array of complications including myopic maculopathy, retinal tears and detachments which causes concern for low vision and blindness [10].

Progression of myopia

Generally, children are born with hyperopic eyes. Emmetropization of eyes occur within first 2 years after birth [11]. Significant changes in the axial length, cornea, and crystalline lens contribute to emmetropization in the early years of life and are usually completed at age 6 years [12]. Factors which interfere with this process and disrupt the balance of anatomical development have been known to cause myopia in both animal and human models [13,14]. Although the exact mechanism is unknown, the occurrence and progression of myopia is determined by a complex interplay of environmental and genetic factors. Environmental factors such as intensive education at a young age are contributory to increased myopia while others, such as increased time doing outdoor activities in bright light have been identified to have a protective effect [15-17]. In 2018, the Ministry of Education in China released a Comprehensive Plan to Prevent Nearsightedness among Children and Teenagers (CPPNCT) to curb myopia among children [18]. In 2023, these guidelines were updated and included reducing electronic device use, adequate lighting in schools, and at least 2 hours of outdoor activities daily [19]. Although the recent increase in myopia has been largely due to environmental changes, genetic factors have been postulated for many years as evidenced by family clustering and twin studies [7,14]. Studies of genetic linkage have identified almost 200 genetic loci for refractive error and myopia, with identified genes having a wide variety of functions thus indicating multigenic and heterogeneous origin [20,21]. However, the rapid increase in myopia over a single generation is inadequate to significantly change the gene pool and thus suggests a greater effect of gene-environment interactions on myopia [13,22].

Myopia is commonly detected in the early school years and usually progresses until around 20 years of age [23]. Children with an earlier onset of myopia were found to have a greater rate of progression than children whose onset were later [24]. This effect is magnified in girls, those of Asian descent, and those with a myopic spherical equivalent [24,25]. Some older children and teens may still show myopic progression but, more commonly, this slows down after 12 to 13 years of age [26]. Minimal axial elongation and myopic progression is observed in the third decade of life [27].

Myopia control

Apart from managing the increasing prevalence of myopia, it is also necessary to mitigate the progression to high myopia and its significant risks to ocular health in individuals. Current treatment strategies for myopia progression address the known mechanisms that work by reducing lag of accommodation, reducing defocus of central and peripheral retina, and blocking myopiagenic signaling [28,29].

1. Spectacles

Bifocal spectacle lenses and progressive addition spectacle lenses were widely used to control myopia. The addition of plus lenses was hypothesized to reduce accommodative demand which was thought to stimulate axial elongation [30,31]. Novel spectacle lenses were designed to reduce peripheral hyperopic defocus, another factor hypothesized to increase axial elongation. Several studies have found statistically significant effects with these treatment options [31,32]. However, effects were minimal and were not considered clinically significant [33-36].

2. Pharmaceutical agents

Atropine is a nonselective antimuscarinic and a long-acting mydriatic and cycloplegic agent. Earliest studies for its use in myopia treatment was first reported in the 1970s [37]. Larger randomized controlled trials including ATOM1 and ATOM2 have investigated different concentrations in different degrees of myopia and its effects on refractive error and axial length [38-40]. Although atropine use in the context of myopia is widely investigated and used, the exact mechanism is still unclear [41]. Common practice of atropine use covers a wide range of concentrations from 0.01% to 0.05%, and less commonly, even higher concentrations [42]. There is no current consensus on the optimal concentration and duration to delay myopia progression but higher concentrations were associated with greater adverse effect such as photophobia, loss of accommodation, blurred near

vision, and allergic reactions [38,43]. A rebound phenomenon was also found wherein discontinuation of atropine in those with myopia progression of greater than 0.5 D/year required greater concentrations upon resuming treatment [28].

3. Behavior

Several studies suggest that outdoor activity time slows both myopia onset and progression [16,44,45]. In a study comparing time spent outdoors and physical activity as predictors of incident myopia, time spent outdoors had a significantly larger effect [16]. Further investigations suggest that the increased level of vitamin D, dopamine, or ultraviolet light during outdoor activities may be contributory to the mechanism of the observed effect on delaying myopia progression [46-48]. A meta-analysis reported an odds ratio of 0.87 for every additional hour of time spent outdoors each day [49].

4. Contact lenses and Ortho-K

Spectacles and contact lenses are common first line options for myopia correction. They are readily available, well-tolerated, affordable, and provide immediate improvement of vision [13]. Variations in contact lenses which aim to deliver peripheral myopic defocus show evidence in delaying myopia progression [50-52]. This is based on the theory that providing additional positive power in the periphery of these lenses creates a myopic defocus in the peripheral retina, causing reduction in axial growth [14]. The effects of soft multifocal contact lenses have also been studied. In the Bifocal Lenses In Nearsighted Kids (BLINK) study randomized controlled trial, high power add (+2.50D) multifocal lenses compared to medium power add (+1.5D) and single vision lenses reduced the rate of myopia progression over 3 years [53]. Further studies for long-term effectiveness and concerns on myopic rebound are necessary [54]. While these lenses rely on manipulating the optical properties of the eye, Ortho-K uses rigid contact lenses which mechanically change the shape of the cornea to correct myopia and decrease its progression.

History of Ortho-K

According to unconfirmed stories, the Chinese put small weights on their eyelids during sleep to improve vision [55]. This concept of mechanically altering the shape of the cornea is the cornerstone of the mechanism of Ortho-K. In the 1950s, polymethyl methacrylate (PMMA) contact lenses were introduced. Because of the rigidity of these lenses, unintended changes of corneal curvature and refractive error became evident specially when these lenses were fitted flatter than the corneal curvature [55]. During its inception in the 1960s, Jessen [56] initially described the "orthofocus" technique for reducing myopia methods [56]. Myopes were fitted with PMMA lenses which fit flatter than the corneal curvature and the resulting tear lens corrected the myopia [40]. After removal of these rigid lenses, the flattening effect persisted and allowed improved unaided vision [55]. Early attempts to correct refractive error lacked data on the corneal topography and were generally based on measured refractive error, thus limiting the effect and efficacy of contact lenses [57]. The technique was renamed "orthokeratology" and was accompanied by further clinical studies in the late 1970s. Corneal flattening control was made by changing the base curve and modifying optic zone diameter, peripheral curves of lens [55]. In the 1980s and 1990s, technological breakthroughs gave Ortho-K significant improvements. Rigid gas-permeable (RGP) contact lenses became more widely available. This type of contact lens reduced the risk of corneal hypoxia and edema, addressing a primary concern for contact lenses that required prolonged overnight wear. Increased customization for patients was achieved with computerized corneal topography and computer-driven lathing systems allowing for improved accuracy. Initially, a series of progressively flatter lenses were used until the desired refractive outcome are achieved [58]. Continued developments in modern Ortho-K allowed for increased molding of the corneal surface, allowing for longer intervals between lens changes. A significant development in modern Ortho-K is the use of a reverse geometry design consisting of a central flat area corresponding to the optical zone surrounded by steeper curve. This design became highly favored because it allowed optimized centration and improved tear exchanges [59].

The U.S. Food and Drug Administration (FDA) approval granted the first approval for an Ortho-K device in 1998 for Contex OK, a rigid RGP for reduction of myopia of up to 3.00D (FDA Summary of Safety and Effectiveness Data: K973697). In 2002, corneal refractive therapy lenses gained FDA approval for myopia of 6.00D with up to 1.75D of astig-

matism [60]. In 2019, MiSight (CooperVision, Inc.) gained pre-market FDA approval for myopia correction and decreasing progression in children aged 8 to 12 at the start of treatment (FDA Summary of Safety and Effectiveness Data: PMA P180035). In 2021, the FDA approved to Acuvue Abiliti (Johnson & Johnson Vision Care Inc.) lenses which reports a decrease in myopia of 1.00 D over a 2-year treatment period. Many improvements have been made to the reverse geometry lenses and lens materials are continuously being improved to abate complications [55].

Mechanism of Ortho-K

Ortho-K lenses are rigid contact lenses that work under the premise that overnight wear can alter the corneal surface, making the cornea flatter and thus temporarily reducing myopia in the daytime (Fig. 1) [61]. Although this flattening effect is temporary, many also use Ortho-K lenses to control myopia progression. It is postulated that visual experience affects the growth of the eye and therefore its refractive capacity. Several theories have emerged attributing this effect to factors such as retinal peripheral defocus, corneal higher order aberrations (HOAs), and changes in accommodative response which seem to regulate axial length elongation [62-65].

1. Peripheral myopic defocus

Peripheral retinal defocus occurs when the central focal point is on the retina while the peripheral focal points are not. In peripheral hyperopic defocus, the peripheral focal points are behind the retina while in peripheral myopic defocus they are in front. Animal studies show evidence of peripheral hyperopic defocus stimulating an increase in axial growth [66,67]. It is worth noting that in myopes, the eye is prolate resulting to a greater degree of peripheral hyperopic defocus [68]. To address this, Ortho-K is designed to create peripheral myopic defocus, in turn decreasing or reversing the stimulus for axial elongation.

MiSight 1 day (omafilcon A; CooperVision, Inc.) is a daily disposable soft contact lens developed for both myopia correction and control of progression. It employs a dual-focus optical design composed of concentric rings with alternating refractive correction zones and peripheral myopic defocus treatment zones. These concentric rings were developed to ensure adequate distance vision as well as peripheral myopic defocus in all gazes. A clinical trial found that use of MiSight slowed axial length growth in treated myopes and, after 6 years of treatment, was found similar to age-matched controls (source 3). Lumb et al. [69] report that these lenses are highly rated in terms of comfort, ease of handling, vision, and satisfaction by children. Although investigations are still underway for this contact lens, the

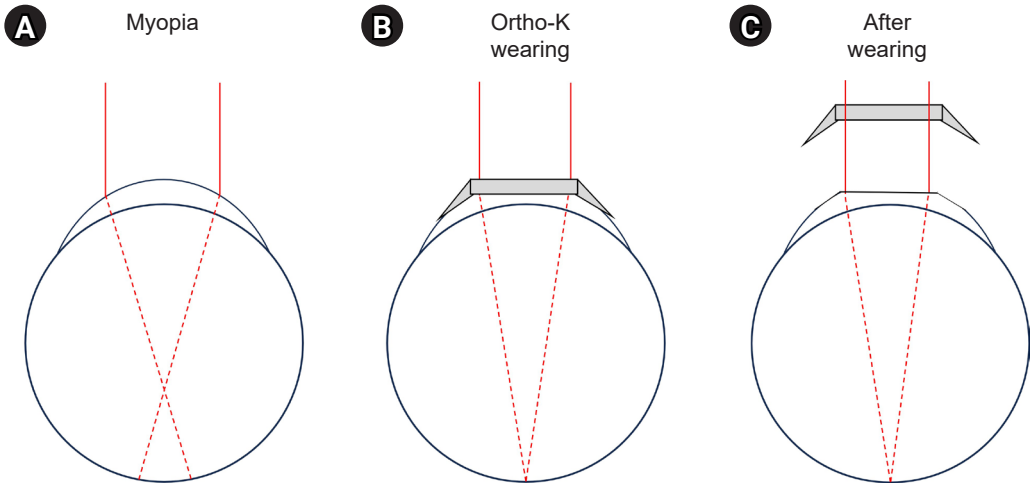

Fig. 1. Overview of orthokeratology (Ortho-K). (A) In myopia, the focus is formed in front of the retina. (B) Ortho-K lenses make the focus form on the retina. (C) After taking off the lenses, the cornea remains flattened and the focus is on the retina

reported outcomes and advantages make it an attractive option for both parents and medical providers [69].

2. HOAs and accommodative response

Apart from peripheral defocus, other HOAs have also been found the affect the regulation of eye growth [70]. HOAs with higher root-mean-square error values lessen accommodative effort and thus decreases the mechanical tension at the equator, leading to slower axial elongation [71]. Some studies reported that more positive spherical aberration and vertical trefoil were associated with less axial growth [71,72]. Ortho-K treatment effectively alters the corneal shape and profile and in turn, increases total HOA that, based on this theory, is desirable in the treatment of myopia progression [73]. Some have attempted to slow axial elongation by using contact lenses that increased spherical aberrations which had modest effects in both children and adults [74]. It is important to note that these lenses induced much smaller spherical aberrations than that of Ortho-K lenses which may not be sufficient to produce the desired effect.

Similarly, another hypothesized mechanism is the improvement of accommodative response. It has been documented that myopic children have greater accommodative lags than emmetropic children, providing another stimulus for myopia progression. Ortho-K is theorized to improve the accommodative response in myopes [75]. However, studies have inconclusive results [76]. In addition to these effects, the use of Ortho-K has been reported to increase subfoveal choroidal thickness which is usually subnormal in myopic eyes [77]. Although the mechanism remains unclear, it is speculated that the use of Ortho-K induces relaxation of large choroidal vessels, increasing blood supply to support choroidal thickening [60,78].

3. Rebound effect

Although Ortho-K shows a significant slowing effect in myopic progression, the results vary with each report and across individuals. As with other modalities of myopia control, rebound effect after discontinuation is an important concern that should be discussed with the patient. It is unclear whether the effects on myopia control are sustained upon discontinuation. Some have reported the potential for this phenomenon with Ortho-K similar to that seen in atropine use [79-81]. The Discontinuation of Orthokeratology on Eyeball Elongation (DOEE) study reported that discontinuation of Ortho-K use before age 14 years led to an increased rate of axial length elongation. Upon reinstitution of treatment after 6 months, the decrease in myopia progression effect is regained although at a slower rate [79]. This may imply that the use of Ortho-K lenses may need to be continued well past age 14 years to achieve an adequate level of control [63,79]. At present, the optimal duration for an Ortho-K treatment regimen is still unknown. Some clinical trials, such as the Longitudinal Orthokeratology Research in Children (LORIC) [82] and the Retardation of Myopia in Orthokeratology (ROMIO) [52] studies conducted in Hong Kong, were conducted over 2 years and showed promising results in decreasing the rates of axial elongation and myopia progression. Previous studies have also reported greater myopia control in the first 2 years of treatment [52,63]. However, data is limited beyond this period. It is widely accepted that further investigation is necessary to optimize this aspect of treatment.

Safety

1. Keratitis

The primary concern with prolonged overnight contact lens use is corneal health. In particular, this environment reduces the ocular surface defense, changes the epithelial surface integrity, and allows bacterial colonization thus increasing susceptibility to microbial keratitis [83]. Reported rates vary but were found to be similar with daily soft contact lens wear [84]. Poor outcomes are usually based on delayed identification and treatment. Majority of cases show positive microbial cultures, with *Acanthamoeba* and *Pseudomonas aeruginosa* being the most common offending agents [85]. Both organisms present with rapidly progressing keratitis, with *Acanthamoeba* keratitis being particularly severe and sight-threatening, often resulting to corneal scarring [17,81]. Early recognition and prompt treatment is necessary to avert these complications. Associated risk factors for keratitis are similar to those for contact lens use including lack of training on proper hygiene, improper fit, use of tap water, poor compliance, and poor follow-up [86]. Care must be made in educating the patient and their guardians of the importance of compliance to proper lens caring regimen, particularly in the context of Ortho-K which is used overnight. This increased risk of a potentially vision-threatening complication must be

discussed with the patient and guardians and must be weighed against the potential benefits.

2. Corneal staining, deposits, and lens associated problems

Corneal staining is most common adverse effect and can present in different patterns with continued Ortho-K use. Some distinctive patterns described are sporadic or diffuse punctate staining, patchy central staining, and whorl-shaped staining [83]. Higher myopia, corneal eccentricity, and smaller corneal horizontal radius can increase the risk of repeated corneal staining episodes [83]. Lens binding is a complication seen with RGPs wherein the contact tear viscosity between the lens and cornea increases during sleep and results in a fluid adhesion force between the two surfaces [87]. Patients may complain that the contact lens feels stuck upon waking up. Forceful removal of the Ortho-K may result in further corneal damage. This may be avoided by using a lubricant before removal. Pigmented ring-shaped corneal deposits resembling Fleischer rings have been reported with Ortho-K use [88,89]. Some suggest that this is caused by stress forces to the epithelium or tear stagnation in the reverse curve area of the lens [88]. It has been reported widely in the Asian population [89] but has also been seen in Caucasian patients [90]. Other lens associated problems are lens tilting and decentration. The treatment zone of Ortho-K lens is important because it compresses the cornea and flatten cornea makes to see well without glasses. Sometimes the factors including increased eyelid tension, corneal astigmatism, movement of lens might cause the lens being out of center [91]. The effort of avoiding this kind of lens associated problems is required before description.

3. Other complications

Other reported but less frequent complications of Ortho-K are bulbar hyperemia, papillary conjunctivitis, corneal edema, palpebral edema, nebular corneal opacity, viral keratoconjunctivitis, band keratopathy, and corneal ulcers. Overall, complications are more common in the first year of use and are less frequent and less severe in children than in adults [92].

Considerations with Ortho-K lens prescription

In Korea, the approximate cost of Ortho-K lenses is USD 1,000. The total cost of treatment increases with each subsequent update or replacement of the lenses after 1 to 2 years. This high cost compared to other treatment modalities like atropine eyedrops may be a financial burden and a barrier to consideration of this treatment.

With overnight use of Ortho-K, it is imperative that careful and regular follow-up be conducted to ensure corneal health and maintain clean contact lenses. For those prescribing Ortho-K, specialized training, certification, and experience are required to become skillful in optimizing lens fitting and management. For the Ortho-K wearer, aside from knowing the benefits for myopia control, they must also be fully aware of the possible adverse outcomes. Lens care and hygiene are critical for maintaining a healthy cornea and minimizing the potential of complications [83,93].

Future of Ortho-K

Although the promising reports regarding Ortho-K use in treatment of myopia, still there are some studies required. Including not only Asian population, but also non-Asians are needed to prove the effect and efficacy of Ortho-K. Further studies are needed about the effective age, period of lens wearing, terms of maximizing stabilization of myopia, potential rebound effect [81]. The education of hand hygiene and warning of safety like corneal infection, opacifications which can cause permanent vision loss. And to evaluate that the effect of Ortho-K is equivalent, noninferior or synergistic effect to low dose atropine on myopia is necessary.

Conclusions

Ortho-K is a treatment modality for the correction of myopia and the slowing of its progression. By addressing different mechanisms of myopia progression, Ortho-K has shown promising outcomes. Rapid advances in this technology have improved the efficacy and safety of prolonged use. However, treatment duration for maximum effect still remains unclear.

Knowledge of the efficacy, safety profile, and limitations of Ortho-K lenses will be invaluable in guiding treatment decisions for both patients and medical professionals.

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Basic knowledge of endoscopic retrograde cholangiopancreatography

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Endoscopic retrograde cholangiopancreatography (ERCP) was first performed in the late 1960s. Due to advancements in instruments, devices, and techniques, ERCP has played an important role in the management and diagnosis of pancreatobiliary disorders. However, ERCP is accompanied by the risk of various complications even if performed by an expert. The incidence of ERCP complications is approximately 4% to 10%, while the incidence of fatal complications, such as death, is less than 0.5%. To prevent adverse events, experts performing ERCP must recognize and address ERCP-related complications and understand the various techniques. In this review, we summarize the complications and techniques of ERCP.

Keywords: Cholangiopancreatography, endoscopic retrograde; Complications; Therapeutics

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP), first attempted in late 1960's, has become the most important procedure for the treatment and diagnosis of various pancreatic disorders and biliary diseases. Moreover, ERCP is actively being implemented in many hospitals. Despite the importance of ERCP, the procedure has the limitation of being high risk compared to endoscopic other procedures and it may be accompanied by various complications. Even ERCP performed by experts cannot completely avoid the occurrence of complications. Thus, to minimize potential complications and ensure the safe execution of the procedure, it is crucial to master various techniques and become well-acquainted with how to manage the diverse complications that may arise effectively. The incidence of ERCP complications is reported to be about 4%–10%, and among these, life-threatening fatal complications are known to be less than 0.5%. In this review, we briefly discuss the comprehensive contents, complications, and coping methods of various guidelines for ERCP, which is an essential procedure in the biliary and pancreatic fields [1-3].

ERCP indication

ERCP can cause several procedure-related complications with severe complications occurring in 0.5% of cases. Hence, selecting patients judiciously is vital, ensuring that the procedure is conducted solely for those who unequivocally require it. In the past, ERCP was used for both treatment and diagnosis; however, with the development of noninvasive endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography, ERCP for diagnostic purposes has not been performed except in special cases

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and is mainly performed for therapeutic purposes only. The indications and contraindications for ERCP, as recognized by the American Society for Gastrointestinal Endoscopy, are listed in Table 1 [4].

Selective biliary cannulation

For the successful performance of ERCP, whether for therapeutic or diagnostic purposes, the first essential step is effective selective biliary cannulation. Selective biliary cannulation does not always guarantee success and is the most common cause of ERCP failure. As the number of biliary cannulation attempts increases, the incidence of ERCP complications also increases.

In a randomized controlled study evaluating the efficacy of selective biliary cannulation using the sphincterotome and ERCP catheter, the success rate was reported as 84% for the sphincterotome, while the ERCP catheter demonstrated a success rate of 62%, indicating a notable difference in performance between the two methods (p<0.05) [5]. The reason for this result is that the sphincterotome has a relatively flexible tip, and the angle of the tip can be adjusted to enable a look-up position; therefore, adjusting the tip to the appropriate axis is advantageous. In addition, the sphincterotome did not demonstrate an increase in complications compared with the ERCP catheter (p=0.30); therefore, selecting the sphincterotome for successful selective biliary cannulation displayed more advantageous results than the ERCP catheter [6].

Table 1. Indications and contraindications of ERCP

ERCP is generally indicated in:	A. Jaundiced patients suspected of having biliary obstruction (appropriate therapeutic maneuvers should be performed during the procedure)
	B. Patients without jaundice whose clinical and biochemical or imaging data suggests pancreatic or biliary tract disease
	C. Evaluation of signs or symptoms suggesting pancreatic malignancy when results of direct imaging (e.g., US, CT, or MRI) are equivocal or normal
	D. Evaluation of pancreatitis of unknown etiology
	E. Preoperative evaluation of patients with chronic pancreatitis and/or pseudocyst
	F. Evaluation of the sphincter of Oddi by manometry
	G. Endoscopic sphincterotomy
	1. Choledocholithiasis
	2. Papillary stenosis or sphincter of Oddi dysfunction causing significant disability
	3. To facilitate the placement of a biliary stent or balloon dilation of biliary stricture
	4. Sump syndrome
	5. Choledochocele involving the major papilla
	6. Ampullary carcinoma in patients who are not candidates for surgery
	7. To facilitate access to the pancreatic duct
	H. Stent placement across benign or malignant strictures, fistulae, postoperative bile leak or in high-risk patients with large unremovable common duct stones
	I. Balloon dilation of ductal strictures
	J. Nasobiliary drain placement to prevent or treat acute cholangitis or infusion of chemical agents for common duct stone dissolution, or to decompress an obstructed common bile duct or postoperative bile leak
	K. Pancreatic pseudocyst drainage in appropriate cases
	L. Tissue sampling from pancreatic or bile ducts
	M. Therapy of disorders of the pancreatic duct
ERCP is generally not indicated for:	A. Evaluation of abdominal pain of obscure origin in the absence of objective findings which suggest biliary or pancreatic disease
	B. Evaluation of suspected gallbladder disease without evidence of bile duct disease
	C. Further evaluation of proven pancreatic malignancy unless management will be altered

ERCP, endoscopic retrograde cholangiopancreatography; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging.
Modified from the American Society for Gastrointestinal Endoscopy [4].

Endoscopic sphincterotomy

Endoscopic sphincterotomy (EST) is a procedure involving cannulation of the sphincterotome into the bile duct via the major papilla and incision using a high-frequency current. According to a meta-analysis comparing ERCP using EST and surgical removal of biliary stones, no statistically significant difference was observed in the biliary stone removal, complication, and mortality rate [7].

According to the European Society of Gastrointestinal Endoscopy ERCP complication guidelines presented in 2020, EST is a high-bleeding-risk procedure and is relatively contraindicated in patients consuming antiplatelet agents, such as clopidogrel, receiving new oral anticoagulants, and patients with acute pancreatitis [8]. According to a large prospective study on nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, the two drugs were not reported to be bleeding risk factors after EST [9]. Additionally, continued administration or discontinuation of antiplatelet medication did not exhibit a statistically significant effect on the occurrence of bleeding after EST (continuation odds ratio [OR], 0.67; 95% confidence interval [CI], 0.21–2.11; withdrawal OR, 1.25; 95% CI, 0.90–1.74) [10]. However, antiplatelet drugs from the non-acetylsalicylic acid group should be discontinued [8].

The risk factors for EST site bleeding include antiplatelet medication use, increased international normalized ratio, decreased platelet count, liver cirrhosis, heart disease, hypertension, and chronic kidney disease [11]. Post-EST bleeding can be prevented by correcting possible risk factors before performing EST [11]. Bleeding risk also varies depending on the type of radiofrequency used during EST. Using a coagulation wave simultaneously, or the Endocut mode is safer than using a cutting wave alone. The simultaneous use of the Endocut mode or coagulation wave has demonstrated a reduction in the risk of zipper cuts, bleeding, and post-ERCP pancreatitis [12]. On the other hand, no difference was observed in bleeding risk depending on the type of sphincterotome used. Moreover, in a comparative study between the blade lengths of 20 mm and 30 mm of the sphincterotome, no statistically significant difference was identified between the two groups [12].

The distribution of blood vessels, especially arteries, in the ampulla of Vater is low at 10% to 11% in the 10–11 o'clock direction. Consequently, research has indicated that maintaining the incision direction of the EST in the 11–12 o'clock direction is preferable to minimize the risk of bleeding [13]. The incision sizes were divided into small, medium, and large. An incision below the transverse fold was classified as a small incision; an incision up to the superior margin of the papillary bulge was a large incision; and an incision in the middle, as a medium incision (Fig. 1).

The superior sphincter of the ampulla of Vater extends into the bile duct in the lateral wall of the duodenum. The middle sphincter is located at the same level as the superior margin of the papillary bulge and protrudes into the duodenal lumen of the ampulla. Therefore, when an incision is made beyond the superior sphincter of the ampulla of Vater, the risk of duodenal perforation increases. To prevent this, incising the ampulla of Vater below the superior sphincter is important.

The high-frequency currents used during EST may interfere with or fail by implantable cardioverter-defibrillators or cardiac pacemakers; therefore, patients with implanted devices should consult a cardiologist before EST [14]. For patients with complete heart block, changing the mode to

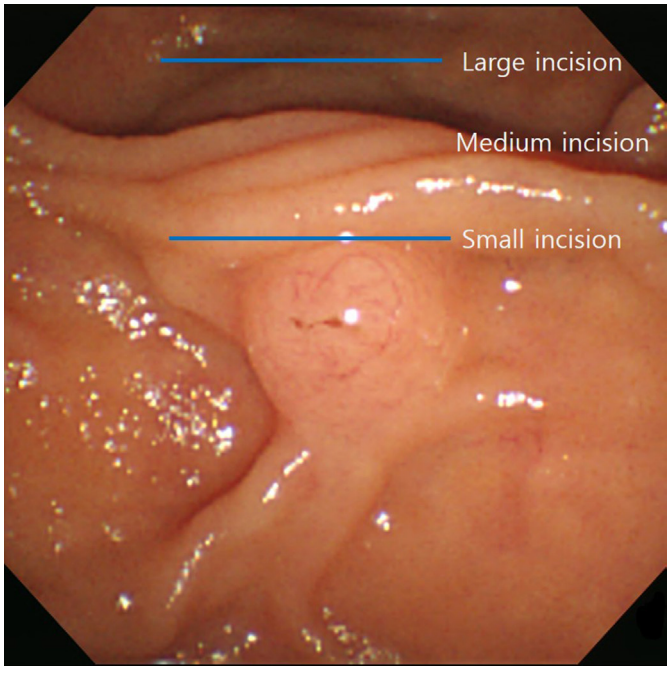

Fig. 1. An incision below the transverse fold was classified as a small incision; an incision up to the superior margin of the papillary bulge was a large incision; and an incision in the middle, as a medium incision.

an asynchronous setting before EST is safe [14]. Additionally, electrocardiography, oxygen saturation monitoring and blood pressure must be performed before, during, and after the ERCP procedure [14].

According to a study on the timing of ERCP in biliary pancreatitis, no statistical difference in the incidence of systemic and local complications was observed (relative risk [RR], 0.59; 95% CI, 0.31–1.11 and RR, 0.86; 95% CI, 0.52–1.43, respectively) in the comparison between the group that underwent ERCP within 72 hours and the group the underwent ERCP after 72 hours following conservative treatment. Similarly, no significant differences were identified in mortality (RR, 0.74; 95% CI, 0.18–3.03) [15]. However, in the case of biliary pancreatitis accompanied by cholangitis, it was reported that systemic and local complications (RR, 0.37; 95% CI, 0.18–0.78 and RR, 0.45; 95% CI, 0.20–0.99) and mortality rates (RR, 0.20; 95% CI, 0.06–0.68) were statistically significantly low in the early ERCP group. Additionally, in patients with cholangitis accompanied by bile duct obstruction, the early ERCP group had a significantly low incidence of local complications (RR, 0.54; 95% CI, 0.32–0.91) [15]. For this reason, performing ERCP early when biliary pancreatitis is accompanied by cholangitis is strongly recommended.

Rescue technique

In cases where selective biliary cannulation is difficult, precutting sphincterotomy is effective in increasing the rate of deep selective biliary cannulation. However, precutting sphincterotomy increases the incidence of perforation and bleeding along with the incidence of post-ERCP pancreatitis [16]. The precutting sphincterotomy was incised from the upper part of the ampulla of Vater, in the proximal or distal direction. The precutting sphincterotomy is attempted in 45%–38% of all ERCPs, and the success rate of selective biliary cannulation is reported to be 35%–96% [17]. Performing precutting sphincterotomy after the insertion of an endoscopic retrograde pancreatic drainage (ERPD) stent allows for an incision of the EST while verifying the direction of the main pancreatic duct, effectively preventing the development of post-ERCP pancreatitis [18]. As precutting sphincterotomy has a higher complication incidence compared to EST, the procedure is recommended when selective biliary cannulation with EST is not possible.

When a guidewire is cannulated in the pancreatic duct during a selective cannulation attempt, selective biliary cannulation using another guidewire without removing the first guidewire is called the double-guidewire technique (Fig. 2). The following three effects can be achieved using the double-guidewire technique: first, straightening of the common channel, second, stabilization of the papilla, and third, moving the guidewire in the distal direction has the effect of opening the bile duct orifice, making biliary cannulation easier [17].

In cases where selective biliary cannulation fails, another rescue technique is the rendezvous technique using EUS, which has recently been actively attempted. After puncturing the extrahepatic bile duct using a 19-gauge needle under EUS guidance, a short guidewire, 260 cm in length, was inserted and passed through the papilla. Next, the scope was changed from EUS to duodenoscopy, and selective biliary cannulation was attempted [19]. According to a retrospective comparative study, the EUS-guided rendezvous technique reported a better biliary cannulation success rate than precutting sphincterotomy (98.3% vs. 90.3%, p=0.03). Additionally, no significant difference was

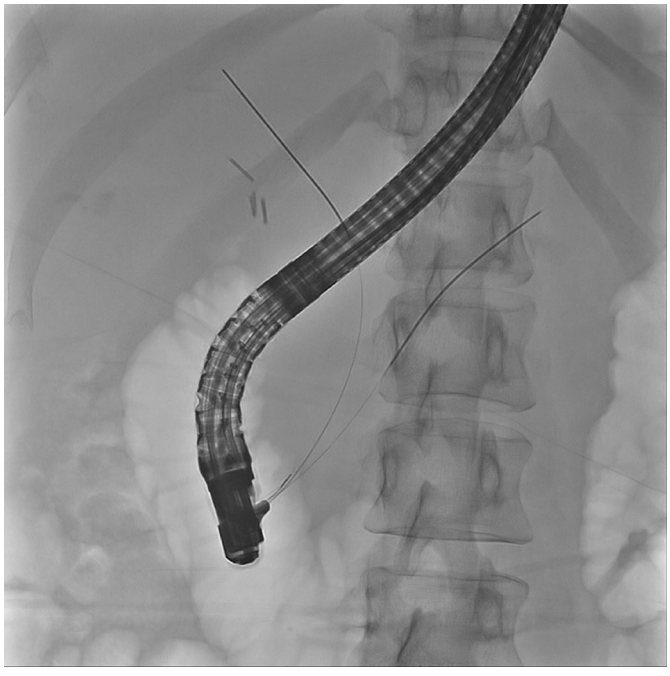

Fig. 2. When a guidewire is cannulated in the main pancreatic duct during a selective cannulation attempt, selective biliary cannulation using another guidewire without removing the first guidewire is called the double-guidewire technique.

observed in complication rates between the two techniques (3.4% vs. 6.9%, p=0.27) [19]. The transgastric approach and short scope position, which involve the observation and puncturing of the bile duct through EUS in the stomach, offer the benefit of enabling the procedure to be performed with a straightened endoscope. Other methods include the transduodenal approach, long-scope position, and the push method. In this method, the procedure is performed by puncturing the bile duct in the duodenal bulb using EUS and then pushing the endoscope along the gastric greater curvature (Fig. 3) [20]. The selection of the puncture location was based on the anatomical condition.

Altered anatomy ERCP

Even in patients with altered gastric and duodenal anatomy due to gastric cancer operation, the EST indication is the same as that in patients with normal anatomy. In patients who have undergone Billroth I type subtotal gastrectomy, EST is performed in the same manner as in patients with normal anatomy. In patients who have undergone Billroth II type subtotal gastrectomy, either a side-viewing endoscope or a forward-viewing endoscope can be used. The choice is determined by the endoscopist's skill level and the patient's anatomy [21]. In cases where access to the papilla is difficult with both a side- and forward-viewing endoscope, the next procedure may be performed after accessing the papilla using a balloon enteroscope [22]. In cases of Billroth II subtotal gastrectomy, a special type of EST knife, such as a push-type sphincterotome, is used as the papilla is accessed from the anal side [22].

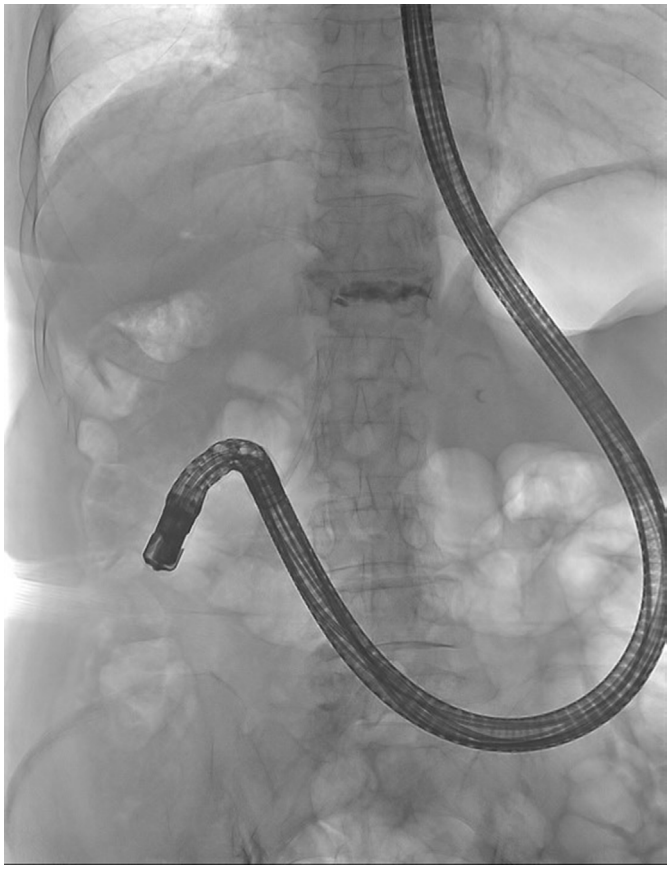

Fig. 3. Pushing the endoscope along the gastric greater curvature.

No significant difference was observed in a randomized controlled trial on the success rate of EST using a needle knife between the side-viewing and forward-viewing endoscopes in patients with altered anatomy (83% vs. 80%). Additionally, no significant difference was observed in EST-related complications [23]. However, complications related to endoscope insertion occurred more commonly with side-viewing endoscopes compared to forward-viewing ones (0% vs. 18%, p<0.05) [23].

In patients who have undergone Roux-en-Y surgery, accessing the papilla using an endoscope of normal length is difficult [24]. In this case, a balloon enteroscopy can successfully access the papilla in 85%–95% of cases [22]. In patients with altered anatomy, the procedure is sometimes performed by expanding the bile duct to 6–8 mm using only endoscopic papillary balloon dilation without EST. In a randomized controlled trial comparing EST and endoscopic papillary balloon dilation alone, no difference in procedure time, frequency of mechanical lithotripsy, or complication rate between the endoscopic papillary balloon dilation and EST groups was identified [25].

Periampullary diverticulum

When the duodenum is accompanied by a periampullary diverticulum, the length and direction of EST must be carefully selected because selective biliary cannulation is difficult and complications easily occur depending on the shape of the papilla and periampullary diverticulum. Bleeding complications occurred more often after EST in patients with periampullary diverticula than in those without periampullary diverticula (8.8% vs. 4.8%, p=0.039) [26].

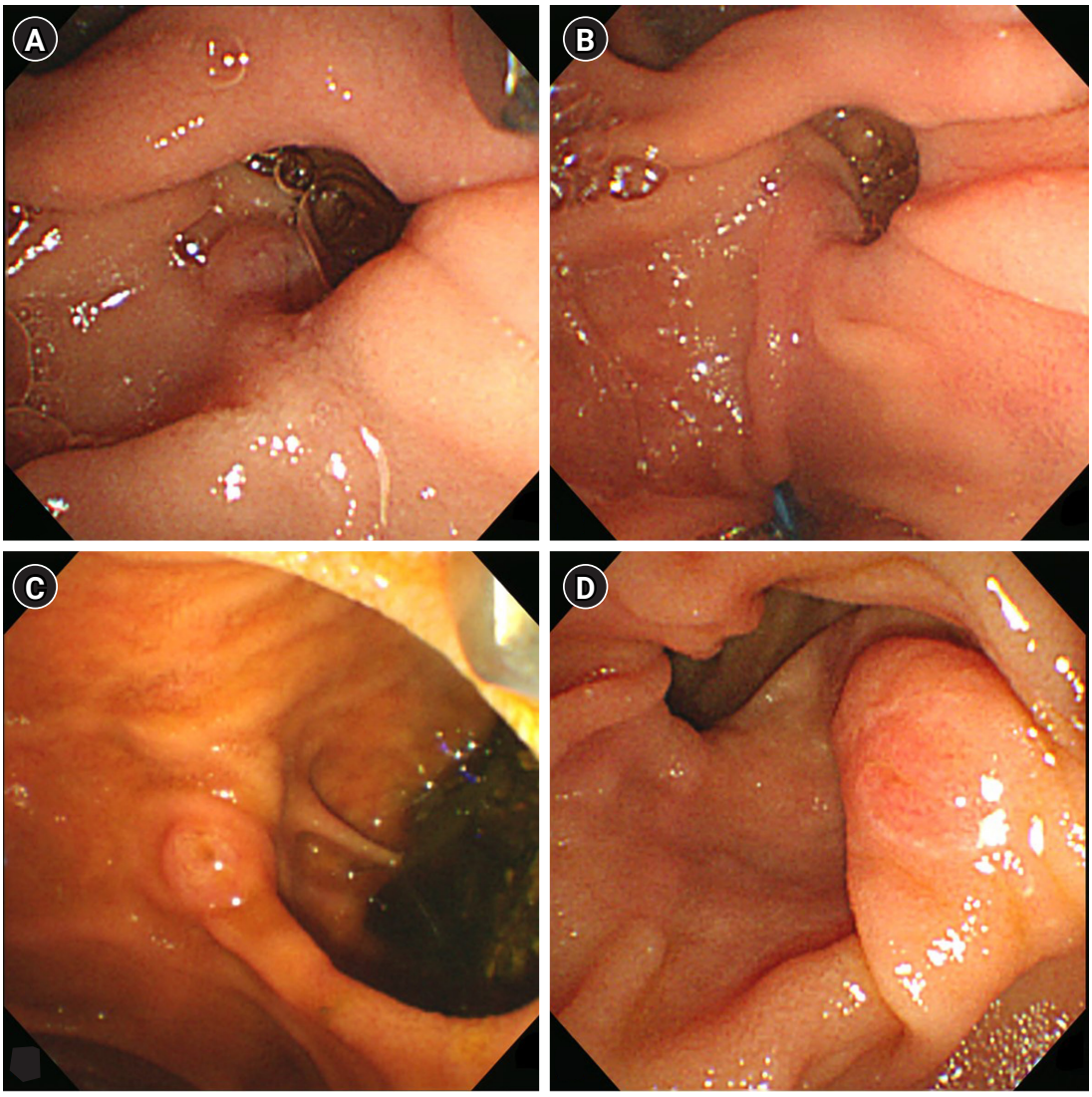

Fig. 4. Periampullary diverticulum types. (A) Type 1, (B) type 1, (C) type 2, (D) type 3.

In particular, when the papilla is located inside a periampullary diverticulum, such as in periampullary diverticulum type 1 (Fig. 4), using the two-devices-in-one-channel method is helpful. The two-devices-in-one-channel method involves inserting forceps for biopsy through the working channel of the endoscope, grabbing the duodenal mucosa, moving it to the distal portion, and moving the papilla outside the periampullary diverticulum to fix it. Subsequently, selective biliary cannulation was attempted by inserting the ERCP catheter through the working channel [27]. Another method involves the use of an endoscopic clip to move the papilla outside the periampullary diverticulum, fix it, and proceed with the procedure [28].

ERCP-related complications

Table 2 displays various complications related to ERCP summarized in the European Society of Gastrointestinal Endoscopy guideline published in 2020 [8]. Early complications related to EST include cholangitis, pancreatitis, perforation, and bleeding. Additionally, complications are reported to occur in 3.0%–11.8% of cases. The incidence of complications is reported to be 0.5%–6.9% for acute pancreatitis, 0%–27.0% for bleeding, 0%–1.8% for perforation,

Table 2. Incidence, mortality, and severity grading of the most common ERCP-related AEs

Type (reference for severity grading)	Incidence	Mortality	Severity grading		
			Mild	Moderate	Severe
Pancreatitis	3.5%–9.7%	0.1%–0.7%	• No organ failure • No local or systemic complications	• Transient (<48 hr) organ failure and/or • Local or systemic complications without persistent organ failure	• Persistent (48 hr) organ failure
Cholangitis	0.5%–3.0%	0.1%	• No criteria of moderate/severe cholangitis	Any of the following: • White blood cell count >12,000 or <4,000/mm^3 • Fever ≥39 °C • Age ≥75 yr • Total bilirubin ≥5 mg/dL • Hypoalbuminemia	Dysfunction of any one of the following (see reference for specific criteria): • Cardiovascular • Neurological • Respiratory • Renal • Hepatic, or • Hematological system
Cholecystitis	0.5%–5.2%	0.04%	• No criteria of moderate/severe cholecystitis	Any one of the following: • White blood cell count >18,000/mm^3 • Palpable tender mass in the right upper abdominal quadrant • Duration of complaints >72 hr • Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)	Dysfunction of any one of the following (see reference for specific criteria): • Cardiovascular • Neurological • Respiratory • Renal • Hepatic • Hematological system
Bleeding	0.3%–9.6%	0.04%	Either of the following: • Abortion of procedure • Unplanned admission <4 nights	Any one of the following: • Unplanned admission 4–10 nights • ICU admission for 1 night • Need for transfusion • Repeat endoscopy or interventional radiology • Intervention for integument injuries	Any one of the following: • Unplanned admission >10 nights • ICU admission for >1 night • Need for surgery • Permanent disability
Perforation	0.08%–0.6%	0.06%	Identical to bleeding	Identical to bleeding	Identical to bleeding
Sedation-related AEs	24.6%	0.02%	Identical to bleeding	Identical to bleeding	Identical to bleeding

ERCP, endoscopic retrograde cholangiopancreatography; AE, adverse event; ICU, intensive care unit.
Adapted from Dumonceau et al. [8] with permission of Georg Thieme Verlag KG.

and 0%–4.2% for cholangitis [8].

1. Post-ERCP pancreatitis

The risk factors related to the occurrence of post-ERCP pancreatitis include pancreatic congestion, increased pancreatic duct pressure due to papillary edema, injection of contrast medium into the main pancreatic duct, damage to the main pancreatic duct due to devices, and thermal damage to the pancreatic duct orifice. The occurrence of post-ERCP pancreatitis is believed to be the result of a complex effect of several factors rather than a single factor [29]. Patient-related risk factors include female sex, young age (<35 years), history of pancreatitis and Oddi's sphincter dysfunction, which are known to be independent risk factors [30]. According to population-based studies, EST has also been reported as an independent risk factor for post-ERCP pancreatitis [31].

Various methods for reducing the occurrence of post-ER-

CP pancreatitis include prophylactic ERPD stent insertion and rectal NSAID suppositories. Administration of pancreatic enzyme inhibitors, somatostatin, octreotide, nitroglycerin, and epinephrine spray to the papilla was ineffective in preventing post-ERCP pancreatitis [32]. The 2020 European Society of Gastrointestinal Endoscopy guidelines recommend that 100 mg of diclofenac or indomethacin should be administered via the transrectal route immediately before the procedure in all patients undergoing ERCP without contraindications [8].

By comparing various NSAID administration routes, only the transrectal route was discovered to be effective [8]. In a study on the timing of NSAID administration, pancreatitis occurred in 6% of patients where NSAIDs were administered before ERCP versus 12% of patients where NSAIDs were administered after ERCP, demonstrating that NSAID administration before ERCP as opposed to after ERCP was more effective in preventing post-ERCP pancreatitis (RR, 0.47; 95% CI, 0.27–0.82) [33]. In patients receiving a single 100 mg dose of indomethacin or clopidogrel, aspirin did not increase the bleeding risk after EST [34].

Additionally, in cases with a high risk of post-ERCP pancreatitis, such as main pancreatic duct cannulation of the guidewire, the double-guidewire technique during ERCP or administration of contrast medium into the main pancreatic duct, insertion of a prophylactic ERPD stent is recommended [8]. In eight meta-analyses published between 2011 and 2019, prophylactic ERPD stent insertion was associated with a reduced incidence of post-ERCP pancreatitis (OR, 0.22–0.39) [8]. Furthermore, in a meta-analysis related to severe post-ERCP pancreatitis, the incidence of post-ERCP pancreatitis was significantly reduced (OR, 0.22–0.26) [8]. Cost-effectiveness analysis displayed that using prophylactic ERPD stent insertion only in high-risk patients was the most cost-effective strategy [8]. For preventive ERPD stent insertion, the use of a flange-type or 5-Fr pigtail-type stent is recommended, and the ERPD stent should be removed within 5 to 10 days [8].

The European Society of Gastrointestinal Endoscopy guidelines also recommend active fluid therapy with lactated Ringer's solution (3 mL/kg/hr during ERCP, 20 mL/kg bolus after ERCP, and 3 mL/kg/hr for 8 hours after ERCP) in patients contraindicated for NSAIDs who are not at risk of volume overload, such as heart failure or renal failure, and who cannot receive an ERPD stent [8].

2. Bleeding

In the 2020 European Society of Gastrointestinal Endoscopy guidelines, the risk factors for bleeding were defined as platelet count <50,000/mm^3, dialysis for chronic kidney disease, anticoagulant use, liver cirrhosis, and bleeding during ERCP [8]. When bleeding occurs, endoscopic hemostasis is considered the first treatment. Severe bleeding requiring transfusion of more than five units of red blood cells or endoscopic hemostasis occurs in 0.1%–0.5% of the cases [35]. Endoscopic hemostasis includes local compression, injection, coagulation, and clipping [36]. Local compression using a balloon catheter or endoscopic papillary balloon dilatation is relatively effective and simple technique. The local hypertonic saline- epinephrine solution is also relatively effective and safe but can cause pancreatitis due to mucosal damage and edema, and perforation can also occur; therefore, caution is required during the procedure [37]. Other methods include heat probing, argon plasma coagulation, and hemostatic clipping, but they must be performed with caution to prevent damage to the main pancreatic duct orifice [38].

3. Perforation

Risk factors for perforation include the precutting method, presence of papillary lesions, dilated bile duct, sphincter of Oddi dysfunction, EST, dilatation of bile duct stricture, and altered anatomy [8]. In particular, retrospective studies have displayed that the anatomy of Billroth II type subtotal gastrectomy is associated with an increased incidence of bowel perforation [39]. If perforation is suspected, abdominal computed tomography should be performed. Perforation requiring surgical treatment occurs in 0.2%–0.7% of cases and death has been reported in 0.2%–0.3% of cases [9]. If the size of the perforation is small, it often improves through conservative treatments such as nasogastric tube drainage, pancreatic duct drainage, and biliary drainage [40]. However, if no improvement is observed within 24 hours of conservative treatment, surgical treatment is required. A delay in the treatment and diagnosis can result in a poor prognosis [40].

Plastic stent or self-expandable metal stent insertion

The 2020 European Society of Gastrointestinal Endoscopy

guidelines recommend not performing routine EST when inserting a single plastic or self-expandable metal stent [8]. Routinely use of prophylactic antibiotics before ERCP was also not recommended. However, antibiotic administration is recommended in cases where incomplete biliary drainage is expected, severe immunosuppression is observed, or cholangioscopy is performed [8]. In addition, it is not always necessary to perform a blood coagulation test before ERCP who do not use anticoagulants and do not have jaundice [8]. In cases of post-ERCP pancreatitis, ERPD stent insertion should be considered only if the patient presents with severe abdominal pain, amylase elevation exceeding 10 times the normal value, or elevated levels of C-reactive protein or white blood cells [8]. If bleeding continues despite general hemostasis after EST, temporary insertion of a fully covered self-expandable metallic stent is recommended [8].

Biliary stone removal rate

A randomized comparative study of the biliary stone removal rates between EST and endoscopic papillary balloon dilation demonstrated that the biliary stone removal rate was higher in the EST group compared to the endoscopic papillary balloon dilation group. Additionally, the biliary stone removal rate during the first session was reported to be 56.2%–92.7%, and the complete biliary stone removal rate was reported to be 86.8%–100% [41]. In the case of a study comparing EST and endoscopic papillary large balloon dilatation, no significant difference was observed [42]. The biliary stone recurrence rate after EST was reported to be 4.1%–17%, the 5-year recurrence rate was 9.6%, and the 10-year recurrence rate was 13.2%. The risk factors for biliary stone recurrence include presence of gallbladder stones, edema within the bile duct, mechanical lithotripsy performed during ERCP, periampullary diverticulum, and dilatation of the bile duct [43]. The recurrence rate of biliary stones increased with the number of recurrences, rapidly rising to 23.4% after the first recurrence and 33.4% after the second recurrence [44]. In case of biliary stone recurrence, treatment through endoscopy is recommended initially. In addition, gallbladder stones can be partially prevented by cholecystectomy [45]. Cholecystectomy is particularly effective in young patients, and the RR is known to be 1.26 for those over 70 years of age, but 3.20 for those under 50 years of age [44]. Incomplete biliary stone removal, age >60 years, previous ERCP, hepatic hilar portion obstruction, and primary sclerosing cholangitis were independent risk factors for the development of cholangitis after ERCP. Conversely, complete removal of extrahepatic bile duct stones reduces the incidence of cholangitis [46].

Conclusions

ERCP is an important procedure in the treatment and diagnosis of various pancreatic and biliary diseases. However, the procedure is difficult, and in rare cases, can cause serious complications. Furthermore, the aforementioned procedure can put the patient at risk if appropriate measures are not undertaken. Therefore, an accurate understanding of biliary and pancreatic diseases should be a priority, and patients suitable for the procedure should be selected. The endoscopist must have appropriate ERCP performance skills, understand various techniques, and perform safe procedures according to the guidelines. Additionally, if a complication occurs, the endoscopist must respond appropriately. In cases where endoscopy is difficult to perform, close multidisciplinary cooperation, such as vascular embolization or surgery, is necessary. In this paper, we have summarized the contents of various ERCP-related guidelines and hope that these will be helpful to doctors performing ERCP in the future.

Summary

ERCP is a basic procedure for the treatment and diagnosis of various pancreatic and biliary diseases. However, ERCP has high-risk factors and may be associated with several complications. Accordingly, endoscopists must have appropriate ERCP performance skills, understand various techniques, perform safe procedures according to guidelines, and respond appropriately to complications that might occur.

Article information

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

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Troponin I and D-dimer levels as triaging biomarkers to distinguish acute pulmonary thromboembolism from myocardial infarction

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Background: Acute pulmonary thromboembolism (APTE) is often confused with myocardial infarction. Previous studies have shown that patients with APTE exhibit lower initial and peak cardiac troponin I (CTI) levels, but higher D-dimer (DD) levels, than patients with myocardial infarction. The present study aimed to reaffirm the tree model algorithm using an entirely new set of data.

Methods: We reviewed retrospective clinical and laboratory data from patients who were diagnosed with APTE or non-ST-elevation myocardial infarction (NSTEMI) between 2015 and 2016. Subjects who were not classified with a diagnosis or did not have their CTI or DD levels assessed were excluded. We categorized patients according to the previous algorithm and compared the outcomes with the previous test dataset.

Results: The analysis involved data from 156 patients with APTE and 363 patients with NSTEMI. In the validation data set, the APTE group showed higher initial DD levels (9.80±10.84 μg/mL) and lower initial CTI levels (0.17±0.54 μg/mL) than the NSTEMI group. The accuracy rate for the test dataset and the validation set were similar. The test set accuracy rate was 91.0%, while the accuracy rate in the validation set improved to 88.6%.

Conclusions: Patients with APTE exhibited lower initial and peak CTI levels, but higher DD levels than NSTEMI patients. The accuracy rate estimates were similar between the test set obtained from the tree model algorithm and the validation set. The study findings demonstrate that the assessment of cardiac biomarkers can be useful for differentiating between APTE and NSTEMI.

Keywords: Myocardial infarction; Pulmonary embolism; Troponin I

Introduction

Acute pulmonary thromboembolism (APTE) can lead to death and is often characterized by symptoms such as chest pain, shortness of breath, and elevated levels of cardiac markers such as cardiac troponin I (CTI) and D-dimer (DD) [1-4]. Our prior research demonstrated that subjects with APTE displayed lower initial and peak levels of CTI, while having higher levels of DD compared to patients with non-ST-elevation myocardial infarction (NSTEMI) [5]. Therefore, the assessment of cardiac biomarkers can be useful for differentiating between APTE and NSTEMI, and the tree model algorithm was previously introduced for this purpose [5]. Pulmonary thromboembolism, such as

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chest pain, dyspnea, and syncope, shares similarities with coronary artery disease, such as myocardial infarction [3,6]. Therefore, when dealing with a patient for the first time, it can be difficult to determine whether to perform a coronary angiogram or a chest computerized computed tomography. We have therefore sought to develop algorithms based on objective markers like CTI and DD.

In this study, our aim was to validate the tree model algorithm in another dataset and investigate a more convenient method of triaging using DD and CTI levels for a differential diagnosis between myocardial infarction and APTE [7].

Methods

Ethical statements: The Institutional Review Board of Dong-A University Hospital granted approval for this protocol (IRB No. DAUHIRB-15-228). The study followed the principles outlined in the Declaration of Helsinki, and the need for informed consent was waived due to the retrospective nature of the chart review design.

1. Data collection and study design

Between January 2015 and December 2016, we gathered historical clinical and laboratory information from individuals who had been diagnosed with APTE and NSTEMI. The presence of APTE was verified through methods such as radionuclide ventilation-perfusion scan, angiography, and chest computed tomography. On the other hand, the diagnosis of NSTEMI was established based on coronary angiography with cardiac biomarkers. Subjects who could not be classified or did not have their CTI and DD levels assessed were excluded. We grouped participants into five different categories based on the tree model algorithm and compared performance to the previous results. The five categories followed the tree algorithm node, and the subjects of the previous study were defined as the test set, and compared with the new validation set recruited in this study.

2. DD assay

The immunoturbidimetric assay enriched with latex is an affordable and swift test, exhibiting analytical sensitivity similar to the traditional enzyme-linked immunosorbent assay (ELISA). To measure DD levels in this study, blood sample taken from a vein was introduced into a test tube containing sodium citrate. Subsequently, the Inovance (Siemens AG) DD assay kit with a Sysmex CS 5100 analyzer (Siemens Medical Solutions) was employed to carry out an immunoturbidimetric assay. A DD concentration of >0.55 mg/L was considered a positive result. For those who had undergone multiple DD evaluations, the initial value obtained before imaging and after the event was used for this analysis.

3. CTI assay

Myocardial ischemia is prevalent among patients with NSTEMI and is indicated by elevated CTI levels. CTI levels were quantified by obtaining venous blood samples in tubes containing heparin and analyzing them twice using the i-STAT system (Abbott Diagnostics). The i-STAT CTI test cartridge used the ELISA method. A CTI concentration of >0.01 μg/mL was considered positive.

4. Description of the tree model algorithm

The tree analysis in this study is a decision tree analysis. It is also known as a tree model. This method is an analysis method that classifies the entire data into several subgroups or performs prediction by representing decision-making rules in a tree structure. It is important to select classification variables and classification reference values at each step of forming a tree structure from an upper node to a lower node. Based on this criterion in the parent node, subnodes diverging from each other are selected so that homogeneity within nodes and heterogeneity between nodes are greatest. Advantages of the tree model include simple structure, easy interpretation, analysis of useful input variables, interaction between predictors and non-linearity, and non-parametric model. In this study, the tree analysis was conducted in R statistical software version 3.4.0.

The algorithm used to discriminate between APTE and myocardial infarction has been described previously [5]. In brief, the algorithm incorporates both baseline high-sensitivity CTI levels and DD levels at the hospital visit. Group 2 is defined as having a baseline CTI level of less than 0.11 μg/mL and a baseline DD level of over 1.5 μg/mL, while group 4 is defined as having a baseline CTI level of less than 0.14 μg/mL and a baseline DD level of over 3.18 μg/mL. The two groups are assumed to reflect APTE. The other groups are more likely to associate with NSTEMI (Table 1, Fig. 1).

5. Statistical analysis

Data analysis was performed using SPSS 18.0 (SPSS Inc.). Data were summarized as mean±standard deviation for continuous variables and percentages for categorical variables. The validation population was divided into APTE and NSTEMI groups according to the previous triaging algorithm using initial DD and CTI levels, with a comparison to confirm diagnosis. The diagnostic performance of the algorithm was tested for sensitivity, specificity, predictive values and the area under the receiver operating characteristic curve. A further triaging system was developed on the basis of the previous algorithm and the results of validation. A *p*-value less than 0.05 was considered to be statistically significant.

Table 1. Diagnostic performance of the algorithm

	Test set (n=123)	Validation set (n=156)
Sensitivity (%)	71.5	73.7
Specificity (%)	96.2	95.0
AUC	0.84	0.84
PPV (%)	83.0	86.5
NPV (%)	92.8	89.4
Accurate (%)	91.0	88.6

AUC, area under the curve; PPV, positive predictive value, NPV, negative predictive value.

Results

1. Study population characteristics

Of the 519 patients who were enrolled in this study, 156

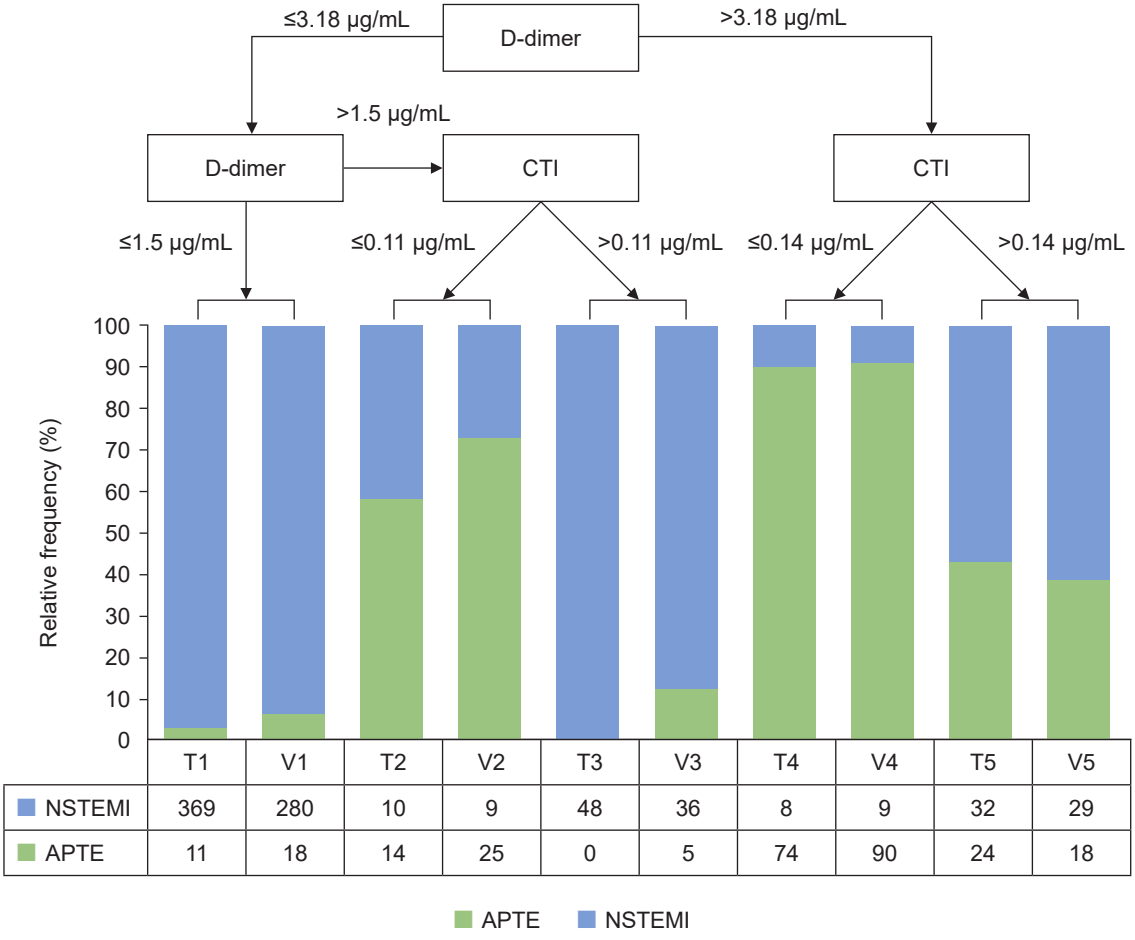

Fig. 1. Validation and diagnostic performance of the previous algorithm. The tree model created five groups. When the validation set was matched to the corresponding group and compared with the previous test set, similarities were noted. NSTEMI, non-ST-elevation myocardial infarction; APTE, acute pulmonary thromboembolism; CTI, cardiac troponin I; T, test set; V, validation set.

APTE patients were diagnosed using chest computed tomography, and 363 NSTEMI patients were diagnosed using CTI, electrocardiogram, and coronary angiography. All subjects had been assessed for baseline DD and CTI levels. In the APTE group, the mean age was 67.7 years old and 48.1% were male. Thirty-two point seven percent of APTE patients had a malignancy and 30.8% of the APTE patients showed concomitant deep vein thrombosis (DVT). The incidence of diabetes, chronic lung disease, and chronic kidney disease was not significantly different between the two groups. The APTE group showed higher initial DD levels (9.80±10.84 μg/mL) and lower initial CTI levels (0.17±0.54 μg/mL) than the NSTEMI group (Fig. 2), similar to previous results. One case of concomitant myocardial infarction and APTE was excluded from the study. The patient baseline characteristics are presented in Table 2.

2. Diagnostic performance of the algorithm

The diagnostic power was verified in an algorithm mentioned previously [5]. Groups 2 and 4 were assumed to be acute pulmonary embolism, while groups 1, 3, and 5 were regarded as myocardial infarction. The accuracy rate was similar between the test data set and the validation set. The test set accuracy rate was 91.0%, and in the validation set, the accuracy saw an enhancement, reaching 88.6%.

3. Easy guidance for further evaluation in patients with chest pain or dyspnea

Based on previous studies and validation data, we have developed several algorithms that can more easily access the first imaging tools with CTI and DD levels in patients with chest pain and dyspnea. Patients suffering from chest pain or dyspnea are more likely to be diagnosed with myocardial infarction if a DD value of less than 1.5 μg/mL is indicated in the emergency room or a first CTI value of greater than 0.1 μg/mL is indicated, so prompt coronary angiography may

Table 2. Study population characteristics

Variable	Test set (n=123)	Validation set (n=156)	*p*-value
Male sex	53 (43.1)	75 (48.1)	0.407
Age (yr)	67.5±11.9	67.7±13.1	0.886
Malignancy	32 (26.0)	51 (32.7)	0.266
History of PTE or DVT	13 (10.6)	1 (0.6)	<0.001
Concomitant DVT	28 (22.8)	48 (30.8)	0.136
Chronic lung disease	11 (8.94)	21 (13.5)	0.240
Diabetes mellitus	24 (19.5)	32 (20.5)	0.836
Hypertension	47 (38.2)	77 (49.4)	0.063
Coronary artery disease	15 (12.2)	24 (15.4)	0.446
Chronic kidney disease	6 (4.88)	17 (10.9)	0.070
Initial D-dimer (μg/mL)	9.83±9.42	9.80±10.84	0.975
Initial C-troponin I (μg/mL)	0.17±0.54	0.19±0.97	0.860

Values are presented as number (%) or mean±standard deviation.
PTE, pulmonary thromboembolism; DVT, deep vein thrombosis.

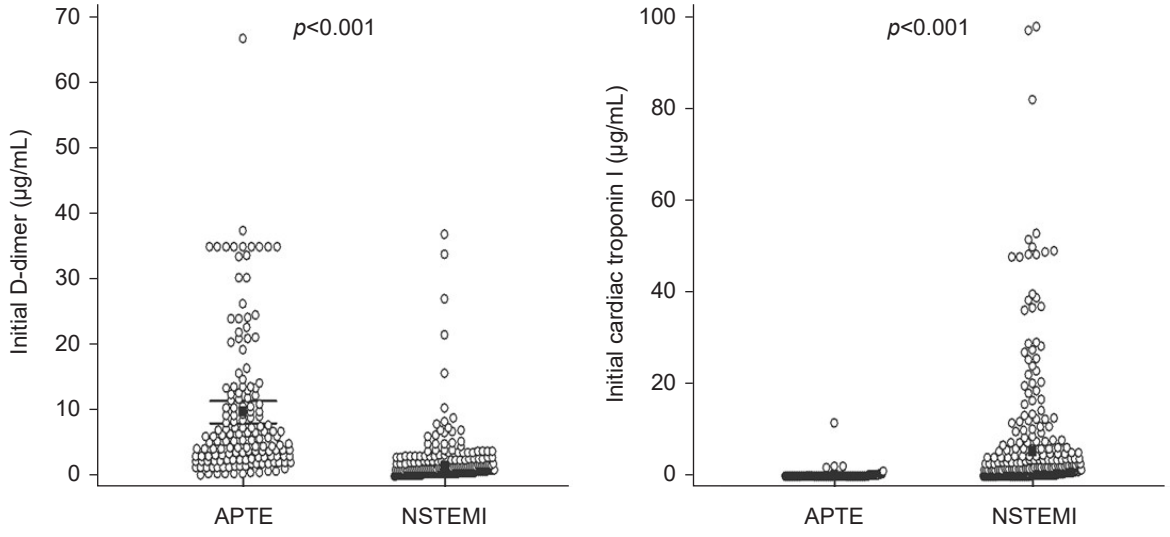

Fig. 2. Initial troponin I and D-dimer level in validation data. APTE, acute pulmonary thromboembolism; NSTEMI, non-ST-elevation myocardial infarction.

be recommended. If the first DD value exceeds 1.5 μg/mL and the CTI value is less than 0.1 μg/mL, the patients may be recommended for chest computed tomography, firstly, for the diagnosis of pulmonary thromboembolism (Fig. 3). It is necessary to further investigate the utility of this technique in the future. However, the aim of this study was to help differentiate between myocardial infarction and pulmonary embolism.

Discussion

This study verified differences in initial CTI and DD levels present in patients presenting with myocardial infarction versus APTE, and appears useful for initial discrimination. Our previous study described the discriminating algorithm used [5]. We have now further proposed guidance for the initial diagnostic strategy in practice where NSTEMI or APTE are suspected, with both conditions requiring rapid diagnosis and management [8,9]. Although clinical characteristics are important in diagnosis, it can be difficult to make decisions dependent on prior diagnostic tests, and whether coronary angiography or computed tomography is needed. We believe the findings in the present study may be helpful for differential diagnosis and initial evaluation using a more simplified classification.

Several previous studies have demonstrated that DD levels increase during myocardial infarction [10], and it has been widely reported that CTI increases during pulmonary embolism and is associated with prognostic outlook [2]. The mechanisms responsible for myocardial infarction and pulmonary embolism are distinct because the mechanisms behind arterial thrombosis and venous thrombosis are also different. CTI and DD levels can be indicative of such differences. The current recommended therapy for pulmonary thromboembolism is thrombolysis and anticoagulation, but because bleeding complication risk is high (similar to the treatment of myocardial infarction), rapid diagnosis is crucial. The clinical features and clinical significance of DD levels in pulmonary embolism reveal that in the group with elevated levels, the actual diagnosis of pulmonary thromboembolism was only 30.6% in the DD-positive group (674 of 2,199 subjects). Conversely, others in the DD-positive group were ruled out as having APTE upon further evaluation or remained as an inconclusive diagnosis. In addition,

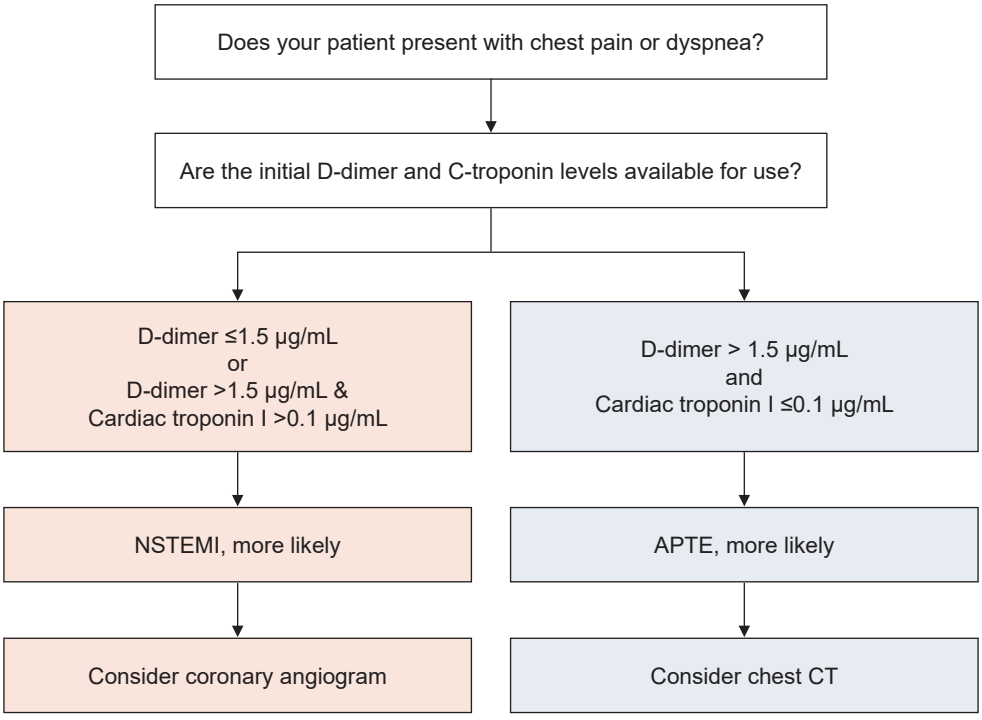

Fig. 3. Decision-making tree for rapid diagnosis of APTE or NSTEMI. APTE, acute pulmonary thromboembolism; NSTEMI, non-ST-elevation myocardial infarction; CT, computed tomography.

five of 1,057 subjects with DD negative status experienced venous embolic events during the 3-month follow-up [11]. Therefore, careful differential diagnosis is important, and it is difficult to exclude APTE mimicking myocardial infarction. Despite efforts to increase the sensitivity and specificity of these diagnoses, in the tree model group 5, when DD >3.18 μg/mL and CTI >0.14 μg/mL, APTE was about 60%, and cases were not well differentiated. This suggests that additional research is needed.

Although the usefulness of the coagulation test (including DD levels) in the diagnosis of myocardial infarction remains controversial, it has been confirmed that it can aid in the differential diagnosis of pulmonary embolism and myocardial infarction [12-19]. In contrast, in critical care units, DD levels are frequently elevated due to heart failure or other diseases, and for this reason it has been reported to be less informative than fast echocardiography [4]. Although early echocardiographic evaluation is also important, there is a limitation associated with emergency screening as delays are common due to a frequent lack of skilled ultrasonographers.

A previous study showed that the ratio of DD to CTI showed better sensitivity and specificity in the differential diagnosis between APTE and NSTEMI than either DD or CTI [20]. The peculiarity of this study emphasized that DD is a test with high specificity in diagnosing APTE in general. The study more focused on sensitivity, but in this study, it would be meaningful to further increase the existing DD specificity through DD and CTI combination.

This study focused on uniform biomarkers, and the clinical data collection was all performed within one university center. All subjects had their diagnoses confirmed by imaging studies. The majority of subjects were verified as having pulmonary thromboembolism by multi-detector computed tomography. Only one case of pulmonary embolism in the test set received a lung perfusion scan for diagnosis. Therefore, the likelihood of over diagnosis or a low detection rate appears low. Previous study reported 40.0% to 50.0% of patients with DVT have APTE, and 90.0% of patients with APTE are diagnosed with DVT. However, in this study, the rate was lower at 30.8%. This study is a retrospective study, and has a limitation of not collecting information on DVT tests in all patients [21]. As this study was performed retrospectively, the patients were not randomized. Some of the NSTEMI and APTE cases showed elevated CTI and D-D levels, and further investigation of these findings is needed.

In conclusion, our findings suggest that the assessment of cardiac biomarkers can be useful when differentiating APTE from NSTEMI. Patients with APTE exhibit lower initial and peak CTI levels, but higher DD levels than NSTEMI patients. In this study, the estimated accuracy rates were similar between the test set derived from the tree model algorithm and the validation set. Patients with DD levels below 1.5 μg/mL or over 0.1 μg/mL of CTI were relatively unlikely to be harboring APTE (specificity 95.3%). These results demonstrate that assessing initial CTI and DD levels can be useful for ruling out APTE in emergency scenarios.

Article information

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

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Author contributions
Conceptualization: MHK. Data curation: SJK, JWL, YSC, DEK, JYH. Formal analysis: KML. Investigation: SJK. Methodology: SJK, KML. Project administration: MHK. Resources: SJK. Software: SKK, KML. Supervision: MHK, JSP. Validation: SJK, KML. Visualization: SJK, KML. Writing – original draft: SJK. Writing – review & editing: SJK, MHK.

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Original article

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Clinical outcomes of prostate artery embolization for management of benign prostate hyperplasia (prostate larger than 100 mL) with or without hematuria

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Background: In this study, we report 1-year follow-up clinical results of prostate artery embolization (PAE) in patients with glandular hematuria or acute urinary retention caused by a large prostate (over 100 mL).

Methods: Twenty-one consecutive patients undergoing PAE from March 2018 to July 2020 were included in this retrospective study. Clinical follow-up was conducted for all patients 1, 3, 6, and 12 months after the procedure. The outcome measures included the International Prostate Symptom Score (IPSS), quality of life (QoL), peak urinary flow rate (Qmax), post-void residual (PVR), prostate volume, prostate-specific antigen, and complications. A *p*-value <0.05 was considered statistically significant.

Results: Twenty-one patients with severe benign prostatic hyperplasia (BPH) with acute urinary retention or prostatic hematuria were enrolled in this study. Technical success rate was 90.5% (19/21), and unilateral PAE was done in 2/21 (9.5%) patients by pelvic vascular obliteration. In all patients, the mean IPSS, QoL score, Qmax, and PVR were significantly improved at 12 months post-PAE. The mean IPSS decreased from 26.1 to 12.1 points ($p<0.05$), mean QoL score decreased from 4.6 to 2.9 points ($p<0.05$), mean Qmax increased from 2.1 to 9.4 mL/s ($p<0.05$), and mean PVR decreased from 300.0 to 70.7 mL ($p<0.05$). The catheter was successfully removed from 19/21 patients and clinical success rate was 90.5%.

Conclusions: PAE was an effective and safe treatment option for patients with BPH and very large prostates (>100 mL) and urinary retention or gross hematuria associated with BPH in men unfit for surgery.

Keywords: Embolization; Hematuria; Prostatic hyperplasia

Introduction

Benign prostatic hyperplasia (BPH) is a benign enlargement of prostate gland and is a major cause of lower urinary tract symptoms (LUTS) in men. Usually, BPH is not life-threatening condition, but it adversely affects quality of life (QoL). Among patients with BPH, LUTS were induced in approximately one in three men, and the clinical progression in 10% despite medication.

Histologically at autopsy, the prevalence of BPH increased to 50%–60% in men in their 60s and gradually increased with age. As the aging society gradually enters, the prevalence of BPH is increasing [1]. So, the better treatment is necessary for growing number of elderly men [2]. Basically, BPH is treated with medical treatment (α-adrenoreceptor antagonists or 5α-reductase inhibitors). If medical treat-

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ment is ineffective, surgical treatment could be considered [3]. Although transurethral resection of the prostate (TURP) is the standard treatment for patient who do not respond to medical treatment, but some patients cannot tolerate TURP for medical (e.g., comorbidity) or technical (e.g., large prostate) reasons [4]. In response to this, interest in minimal invasive surgery with less morbidity is increasing [5-7].

As the number of elderly patients increases and the number of comorbidities they have, the number of patients taking anticoagulants is increasing. Along with this phenomenon, the proportion of patients with enlarged prostate and hematuria is increasing. Prostatic origin gross hematuria usually resolved conservative measures but, in refractory hematuria cases especially in large prostate hyperplasia, prostate artery embolization (PAE) could be a good option [8].

As a form of minimal invasive treatment, PAE treatment was introduced in 2010 [9]. PAE is an interventional radiological technique that directly occludes the prostate artery and causes prostate infarction. The effectiveness and safety of this technique have already been demonstrated following its initial clinical implementation. However, there are not much data on the clinical effect of PAE in cases of very large prostate (>100 mL). In this study, we report 1-year follow-up clinical results of PAE in patients with glandular hematuria or acute urinary retention (AUR) by large prostate (over 100 mL).

Methods

Ethical statements: This study was approved by the Institutional Review Board of Dong-A University Hospital (IRB No. DAUHIRB-19-026) and was conducted in accordance with the recent Declaration of Helsinki. Informed consent was waived.

From January 2018 to December 2020, at a single-center, 21 consecutive patients who received PAE were retrospectively reviewed under an institutional review board approved protocol and ethical issues were considered [10].

Included patients were who had gross hematuria or AUR due to larger than 100 mL prostate. All patients underwent evaluations of medical and surgical history, International Prostate Symptom Score (IPSS), QoL index questionnaire and Charlson Comorbidity Index. Peak urinary flow rate (Qmax) and post-voiding residual urine volume were recorded. Also, pre-procedure prostate-specific antigen (PSA) and prostate volume (PV; transrectal or transabdominal ultrasound) were obtained. The prostate biopsy was performed for distinguishing prostate cancer when PSA level was above 4.0 ng/dL. In patients with gross hematuria, urine cytology, ultrasound of the kidneys, ureters & Bladder, and cystoscopy were performed to discriminate urinary tract malignancy, also. Exclusion criteria for PAE included biopsy proven prostatic cancer, active prostatitis or urinary tract infection, previous surgical procedure or other invasive treatment for benign prostate hyperplasia, large bladder diverticula or bladder stones, and chronic renal failure.

1. Follow-up and outcome evaluation

Clinical follow-up was done in all patients 1, 3, 6, and 12 months after the procedure. Outcome measures included IPSS, QoL, Qmax, post-void residual urine volume (PVR), PV, PSA, and complications. A p-value <0.05 was considered statistically significant. The technical success was defined as bilateral successful PAE. Clinical success was defined as improvement of LUTS. The LUTS was assessed by using IPSS and QoL questionnaires or self-voiding was possible in men with urinary retention prior to PAE. Clinical failure was considered a case where self-voiding was impossible after indwelling catheter removal.

2. Procedure

Angiography and PAE were performed by one interventional radiologist on an inpatient basis at the interventional radiology suite (Allula Clarity FD 20; Philips Healthcare) equipped with the cone-beam computed tomograhpy (CBCT) option (XperCT; Philips Healthcare) after patients have signed informed consent. The procedure was performed via the right femoral arterial access under local anesthesia. Initial pelvic angiography was performed using a power injector to evaluate iliac vessels and the prostate arteries during arterial and late phases. Then, selective bilateral internal iliac arteriograms were obtained using a 5-French Robert's uterine artery catheter (RUC catheter; Cook) in the anterior-posterior view. CBCT was performed with the 5-French RUC catheter located in the main trunk of internal iliac artery in the same tip of the catheter as was used with digital subtraction angiography to evaluate the origin of the prostate arteries. Prostate arteries for each side were identified by using vessel-tracking software (EmboGuide; Philips Healthcare) applied to the CBCT datasets. The

software allowed the automated extraction of candidate vessels between a user-selected starting point (the catheter tip) and a segmented target (the prostate). Super-selection of each prostate artery was performed by using microcatheter (Veloute 1.7; Asahi) and microguidewire (Meister 0.016; Asahi) in the best aspect (ipsilateral oblique perspective, 25°–55°) to identify the prostate artery under the roadmap technique. Then, prostatic arterial digital subtraction angiography was performed by manual injection in the anterior-posterior and same ipsilateral oblique view. Embolization was performed using 250 to 355 non-spherical polyvinyl alcohol particles (Contour; Boston Scientific) in all patients. Contour was diluted in 20 mL of normal saline and 30 mL of contrast medium in a 2:3 solution. The mixture was slowly injected through 1-mL syringe under fluoroscopic guidance until we reached an end point of near stasis of contrast agent without reflux of embolic agent.

3. Statistical analysis

The categorical variables were presented as numbers and frequencies and continuous variables were presented as mean±standard deviation or median and interquartile range. For trend analysis, repeated measure analysis of variance was used for IPSS, QoL, Qmax, PVR, PSA, and PV. All tests were two-sided, and p-values <0.05 were considered statistically significant. Analyses were performed using SPSS statistics v 18.0 for Window (IBM Corp.).

Results

Twenty-one patients with severe BPH with AUR or prostatic hematuria were enrolled in this study. Patients' basic demographic data are presented in Table 1. Bilateral PAE was technically successful in 19 out of 21 patients (90.5%), and unilateral PAE was done in two out of 21 patients (9.5%) by pelvic vascular obliteration.

Patients were followed for at least 12 months. Patient data before and after PAE are presented in Table 2. In all patients, the mean IPSS, QoL score, Qmax, and PVR were significantly improved at 12 months postoperatively (Table 2). The mean IPSS decreased from 26.1 to 12.1 points (p<0.05), mean QoL score decreased from 4.6 to 2.9 points (p<0.05),

Table 1. Baseline clinical characteristics of participants prior to PAE

Characteristic		Value (n=21)
Age (yr)	Mean±SD	72.6±4.7
	Median (IQR)	72 (65–75)
Charlson Comorbidity Index	Mean±SD	6.1±1.2
	Median (IQR)	6 (5–7)
IPSS	Mean±SD	26.1±4.3
	Median (IQR)	26 (24–28)
IPSS-QoL	Mean±SD	4.6±0.5
	Median (IQR)	4 (4–5)
Post-void residual urine volume (mL)	Mean±SD	300.0±112.8
	Median (IQR)	280 (230–350)
PSA (ng/mL)	Mean±SD	7.4±3.8
	Median (IQR)	6.2 (4.1–9)
Prostate volume (mL)	Mean±SD	118.1±15.1
	Median (IQR)	119 (107–130)
Comorbidity, No. (%)		
Cerebrovascular accident		6 (28.6)
Diabetes mellitus		10 (47.6)
Coronary heart disease		3 (14.3)
Gross hematuria, No. (%)		8 (38.1)
Pre-PAE catheterization due to AUR, No. (%)		17 (81.0)

PAE, prostate artery embolization; IPSS, International Prostate Symptom Score; QoL, quality of life; PSA, prostate-specific antigen; AUR, acute urinary retention; SD, standard deviation; IQR, interquartile range.

Table 2. Summary of the mean changes from baseline at 1, 3, 6, and 12 months

Variable	Pre-PAE	1 mo	3 mo	6 mo	12 mo	*p* for RM
IPSS						<0.05
Mean±SD	26.1±4.3	14.1±3.0	13.1±3.2	12.8±3.4	12.1±3.1	
Median (IQR)	26.0 (23.5–29.0)	13.0 (13.0–15.5)	12.0 (11.0–14.0)	11.0 (10.5–15.0)	12.0 (10.0–13.5)	
QoL						<0.05
Mean±SD	4.6±0.5	2.7±0.9	2.8±0.9	2.8±0.9	2.9±0.8	
Median (IQR)	5.0 (4.0–5.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	
Qmax (mL/s)						0.004
Mean±SD	2.1±1.9	12.1±17.2	8.9±1.9	9.1±1.7	9.4±1.9	
	2.7 (0.0–3.5)	8.5 (7.3–10.0)	9.3 (7.9–10.2)	9.0 (8.5–10.4)	9.0 (8.9–10.5)	
PVR (mL)						<0.05
Mean±SD	300.0±112.8	85.0±40.6	74.3±37.4	73.4±31.8	70.7±29.5	
Median (IQR)	280.0 (225.0–375.0)	75.0 (56.0–95.0)	75.0 (45.0–88.0)	65.0 (52.5–85.0)	64.0 (57.0–76.5)	
PSA (ng/dL)						<0.05
Mean±SD	7.4±3.8	6.0±1.7	5.2±1.9	3.4±0.7	3.3±0.6	
Median (IQR)	6.2 (4.0–10.0)	6.0 (4.5–7.0)	5.0 (3.9–6.5)	3.5 (2.8–3.8)	3.2 (3.0–3.7)	
Prostate volume (mL)						<0.05
Mean±SD	118.1±15.1	-	94.5±12.0	87.1±12.1	79.5±15.1	
Median (IQR)	119.0 (105.0–130.0)	-	95.0 (84.0–104.0)	87.0 (77.0–95.0)	78.0 (70.0–83.0)	

PAE, prostate artery embolization; RM, repeated measure; IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, peak urinary flow rate; PVR, post-voiding residual urine volume; PSA, prostate-specific antigen; SD, standard deviation; IQR, interquartile range.

mean Qmax increased from 2.1 to 9.4 mL/s (p<0.05), and mean PVR decreased from 300.0 to 70.7 mL (p<0.05). Furthermore, the mean prostatic volume and mean PSA level decreased from 118.1 to 79.5 mL (mean reduction of 32.7%, p<0.05) and 7.4 ng/dL to 3.3 ng/dL (p<0.05), significantly (Fig. 1).

The catheter was successfully removed from 19 of 21 patients and clinical success rate was 90.5%. Seventeen patients were able to remove the catheter after 1 week of the procedure. However, two patients needed additional 2 weeks of catheter placement. Median hospital stay was 2 days. Two patients could not void after PAE, they diagnosed as a detrusor underactivity by urodynamic study. Eight patients with hematuria had controlled of bleeding following the embolization in all patients.

Adverse events were summarized in Table 3. There were no major complications (>3 Clavian complications) and nontarget embolization. Nine patients had minor complications. Four patients (19%) had a urinary tract infection, and they were controlled by 2 weeks of antibiotics. Two patients (9.5%) felt a burning sense of the perineum and they were controlled by nonsteroidal anti-inflammatory drug (NSAID) only. Three patients developed urge incontinence after removed catheter. They needed 2 to 3 diapers per day immediately after removed catheter for managing urge incontinence, but this symptom was resolved by conservative care with anticholinergics.

Discussion

The patients with a prostate larger than 100 mL had limited treatment options. Traditionally, surgery (simple prostatectomy) has been considered as treatment of choice. But these have a relatively high risk of adverse events like that bleeding and postoperative incontinence [1,2]. In addition, endoscopic approach using Holium or Thulium laser (Holium laser enucleation of prostate and Thulium laser enucleation of prostate) has been widely used as the development of minimal invasive treatment. However, endoscopic laser enucleation also has many difficulties that necessity of anesthesia, bleeding, incontinence, urethral stricture, or retrograde ejaculation etc. in applying to all large BPH patients, and steep learning curve [11-14]. Nowadays PAE has been considered as another minimal invasive treatment of option for who could not be suited to surgery.

Patients included in this study had difficulties in surgery

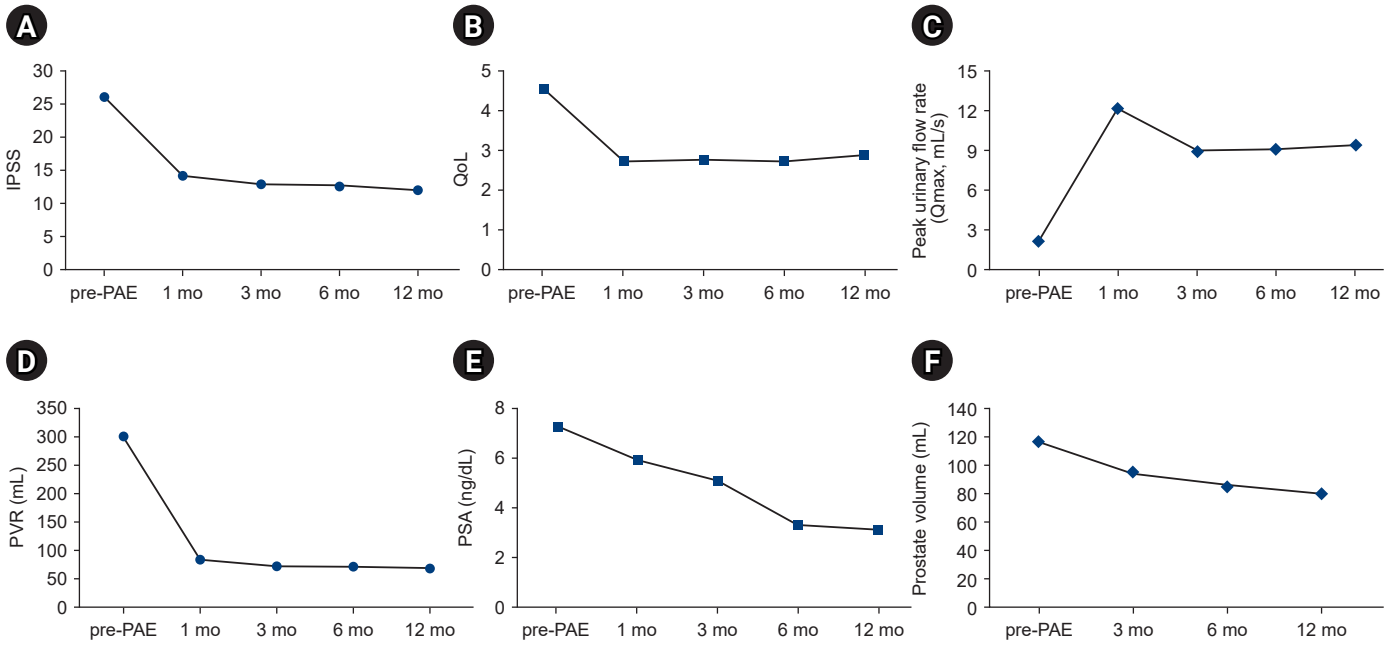

Fig. 1. Comparisons of the following parameters from the preoperative assessment through 1, 3, 6, and 12 months postoperatively: (A) mean International Prostate Symptom Score (IPSS); (B) mean quality of life (QoL) score; (C) mean peak urine flow rate (Qmax); (D) mean post-void residual (PVR) urine volume; (E) mean prostate-specific antigen (PSA) level; and (F) mean prostate volume. PAE, prostate artery embolization.

Table 3. Adverse events (n=21)

Minor complication	No. (%)	Managements
Urinary tract infection	4 (19.0)	2 wk antibiotics
Urge incontinence	3 (14.2)	Anti-cholinergic medication
Pelvic pain	2 (9.5)	NSAID with conservative care

NSAID, nonsteroidal anti-inflammatory drug.

or anesthesia due to comorbidity, 13 out of 21 (61.9%) patients taking anticoagulant due to previous coronal heart disease or cerebrovascular accident. And seven patients (33%) had gross hematuria, also.

Recent papers have shown good results for the treatment of large prostates with PAEs, with prostate size reductions of 32% to 45% over 12 months, and 57% to 68% of the IPSS and QoL improved [15-19]. Feng et al. [20] performed a meta-analysis that reported the efficiency and safety of PAE and indicated that the IPSS and QoL scores showed great improvement after PAE (p<0.05). In present study, the PV reduction rate was 32.7% (from 118.1 to 79.5 mL) and IPSS decreased from 26 points to 12 points (–53.6%) after 12 months of observation. Besides these, other monitored functional results (QoL, PSA, post-voiding residual urine volume, and urine flow rate) were significantly improved at 12 months post-PAE, like the results reported by Gao et al. [21]. Furthermore, Lebdai et al. [22] reported mean IPSS reduction was 11.9 points at post-PAE 1 month, which was maintained post-PAE 6 months.

In this study, IPSS and QoL at 1 month were improved and which was persisted for 12 months, also. PV showed a significant reduction at 3 months post-PAE, and it was maintained continuously for 12 months (Fig. 1). Pisco et al. [23] reported that the post-PAE PV reduction was related to clinical efficiency. These clinical results are presumed to be related to the histopathologic degeneration of the prostate by occluding the prostate vasculature [24].

Additionally, a study investigating PAE specifically in catheter-dependent patients with large BPH showed 86% success in catheter removal in mean of 18.2 days after procedure [11]. In this study, mean catheterization date was 7.7 days and 90.4% (19/21) catheter free rate, also. Catheter were removed after 1 week of PAE procedure in outpatient clinic. After removal of the catheter, four patients could not void and maintained an additional catheterization for 2

weeks. After 2 weeks of additional catheterization, two patients were able to void, but two patients were still unable to void, and they needed intermittent catheterization. These patients were checked urodynamic study and diagnosed as detrusor underactivity.

In our study, PAE was performed by a single radiologist who had enough experience, and 21 cases were performed successfully. Most studies used computed tomograhpy angiography or magnetic resonance angiography prior to the intervention to identify the prostatic artery [23,25-31], and CBCT was usually performed only to rule out nontarget embolization. We checked CBCT before embolization in all patients [31,32]. For achieving optimal outcome bilateral PAE is important [33]. CBCT can help reduce the risk of embolization by visualizing the prostate arteries to help identify collateral supply vessels. We defined technical success as accomplished bilateral PAE, can be achieved at 90.5%. Two patients had pelvic vascular obliteration by atherosclerosis, so we did unilateral PAE.

PAE is a relatively safe method except for possible mis-embolization, there is no expected major complication. In recent meta-analysis found that major complication rate was 0.3% due to nontarget embolization, and the most common minor complications were dysuria (17.0%) and transient increased urinary frequency (11.6%) [34]. In this study, adverse events were summarized in Table 3. There were no major complications (>3 Clavian complications) and nontarget embolization. Nine patients had minor complications. Four patients (19%) had a urinary tract infection, and they were controlled by 2 weeks of antibiotics. Two patients (9.5%) felt burning sense of the perineum and they were controlled by NSAID only. Three patients developed urge incontinence after removed catheter. They needed 2 to 3 diapers per day immediate after removed catheter for managing urge incontinence, but this symptom was resolved by conservative care with anticholinergics.

Limitations of this study include the single-center, retrospective fashion, which may decrease the quality of evidence. Second, the sample size of patients was small and there was a selection of bios. This small sample size probably influenced the results of this study to obtain relatively better results compared to other studies. Additionally, we reported the results of 1-year follow-up, but the follow-up period was not sufficient. Despite the small sample size and insufficient follow-up period, reduction in prostate size and improvement of LUTS were confirmed in patients with an enlarged prostate greater than 100 mL at risk of surgery, and the clinical usefulness of PAE was confirmed. In the future, additional studies are needed on the efficacy of PAE in the enlarged prostatic hyperplasia of the median lobe and small benign prostate hyperplasia patients.

In conclusion, PAE could be a secondary option for treating large BPH (over 100 mL) and urinary retention or gross hematuria associated with BPH in men unfit for surgery. Proper patient selection through evaluation is especially important to ensure clinical success.

Article information

Conflicts of interest

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

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Author contributions

All the work was done by SK.

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Initial experience with Retzius-sparing robot-assisted radical prostatectomy compared to the conventional method: is it a suitable option for robotic prostatectomy beginners?

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Background: Retzius-sparing robot-assisted radical prostatectomy (rsRARP) is a surgical procedure that can minimize the resection of surrounding prostate tissue by enabling access through the anterior surface of the Douglas pouch. We reported our initial experiences with rsRARP compared to conventional robot-assisted radical prostatectomy (RARP).

Methods: Retrospective data were collected from March 2019 to June 2022, including 69 patients who underwent robotic radical prostatectomy for localized prostate cancer. The operations were performed at a single center, and we alternated between the two methods. Perioperative characteristics and oncologic and functional outcomes were analyzed.

Results: In total, 35 patients underwent RARP and 34 patients underwent rsRARP. The preoperative characteristics of the patients were similar. Oncologic and functional parameters were analyzed postoperatively. Except for early recovery of urinary incontinence (immediate, 1 month, 3 months, 6 months: $p<0.001$, $p=0.002$, $p=0.004$, and $p=0.014$, respectively), there were no significant differences between the two groups. We also analyzed trends in operation time and oncologic and functional outcomes according to the progression of rsRARP cases.

Conclusions: rsRARP has the major advantage of enabling an early recovery from urinary incontinence after surgery, and it is also a good surgical approach that shows oncologically similar results to the conventional approach. It is also highly reproducible and can be recommended to surgeons new to robotic radical prostatectomy.

Keywords: Prostate cancer; Prostatectomy; Prostatic neoplasms; Urology

Introduction

Since laparoscopic radical prostatectomy was first described by Schuessler in 1992, the most popular surgical approach to prostate cancer today involves making an incision toward the anterior wall of the bladder to access the anterior wall of the prostate for removal [1].

In 2000, Binder and Kramer [2] and Abbou et al. [3] first performed and reported on robot-assisted radical prostatectomy (RARP). As the procedure evolved, it became possible to overcome its previous difficulties. Since then, robotic surgery has become the main surgical option for

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localized prostate cancer due to advances in anatomical understanding and techniques, such as bladder neck preservation, nerve-sparing techniques, and prostate apex management. This also made it easier to resect the prostate and re-anastomose of the urethra, which is difficult to access with a laparoscopic approach. As technology advances, interest in surgical outcomes has increased, three important factors in the surgical outcome of prostate cancer were proposed around 2005: cancer control, continence, and potency [4]. After 24 months, the proportion of participants that satisfied all three was reported to range from 50% to 60%. It is not easy to achieve both satisfactory oncological and functional results; nevertheless, steady attempts have been made to achieve both in patients with prostate cancer.

In 2010, Galfano et al. [5] announced a new approach to robotic prostatectomy. The Retzius-sparing RARP (rsRARP) accesses the prostate through the Douglas pouch. The surgeon begins dissecting from the prostate base around the seminal vesicle without resecting any of the anterior compartment of the bladder or the prostate. This preserves the neurovascular bundle, endopelvic fascia, Aphrodite's veil, Santorini plexus, and pubourethral ligaments, which the authors argue provides a better functional outcome.

In 2014, Lim et al. [6] published a study comparing the initial experience of rsRARP with conventional RARP and reported that the oncological results were not significantly different from those of conventional techniques, showing only advantages in reducing console time and early recovery of continence. Therefore, we reported on the initial experience and outcomes of rsRARP compared with conventional method.

Methods

Ethical statements: The study was approved by the Institutional Review Board (IRB) of Kosin Medical Center (IRB No: KUGH 2023-06-015). Informed consent was waived.

1. Participants and trial design

From March 2019 to June 2022, the medical records of 69 patients who were diagnosed with localized prostate cancer who underwent RARP were reviewed retrospectively. Prostate cancer was confirmed preoperatively by prostate biopsy. Patients with metastases in subsequent examinations and previous transurethral prostate surgery were excluded from the study. The rsRARP was performed by a surgeon with fewer than 10 robotic prostatectomy cases in a single center. Prior to surgery, the patient underwent a complete blood count, magnetic resonance imaging of the prostate, bone scan, etc. The length of hospital stay followed our protocol, and the Foley catheter was generally removed 1 week after surgery. Age, initial prostate-specific antigen (PSA), D'Amico risk group, biopsy Gleason score, console time, estimated blood loss, pathologic stage, pathologic Gleason score, postoperative complications (Clavien-Dindo classification), postoperative continence, potency, positive surgical margin (PSM), and biochemical recurrence (BCR) were evaluated.

2. Definition

Since total operative time includes time taken for other tasks, such as anesthesia and patient preparation, console time was easier to compare and also more accurate. Complications were classified according to the Clavien-Dindo system. Recovery of urinary continence was determined when the patient no longer required incontinence pads. Follow-up was immediate and then 1 month, 3 months, 6 months, and 12 months after catheter removal. Potency was defined as being able to erect sufficiently for insertion. BCR was evaluated 1 year after surgery and was diagnosed when the PSA was elevated above 0.4 ng/mL.

3. Surgical technique

The surgeons had experience with several conventional methods, including open radical prostatectomy and laparoscopic-assisted radical prostatectomy. RARP was performed when the robot was introduced to our hospital in May 2017, and rsRARP was first performed in March 2019. There was no difference in the surgical method between the previously performed laparoscopic-assisted radical prostatectomy and conventional RARP, and it was performed based on the method of Menon et al. [7]. However, ligation of the vas deferens through the anterior portion of the Douglas pouch and dissection of the seminal vesicle were performed first before the anterior bladder dissection. Meanwhile, rsRARP was performed for the first time by another surgeon who had only a few RARP cases. The Retzius-sparing technique was performed with reference to the Galfano approach and Rha's live surgery in 2018 [5,6]. The rsRARP method included the following modifications.

The patient was placed in a standard 30º Trendelenburg position under general anesthesia. A four-arm Da Vinci robot Xi (Intuitive Surgical) was used. The patient cart was accessed from the bottom of the table or the left side of the patient. There was no difference in difficulty of the operation according to location of the patient cart. Five total trocars were used; the one for the laparoscope was placed horizontally within the umbilicus. The four robot trocars were 7 mm in diameter; one right and two left trocars were positioned at 7-cm intervals from the left and right relative to the camera port in the umbilicus. The assist port was positioned to the right side of the robot port as a 12-mm diameter port and was used for suction and traction, insertion and removal of suture material, and insertion of a specimen bag. The Prograsp, Maryland bipolar forceps, and monopolar curved scissors were inserted from the left into the robot port.

The sigmoid colon was moved toward the head, and the bladder was pushed upward to expose the Douglas space more clearly. The parietal peritoneum above the seminal vesicles was incised horizontally. Both seminal vesicles and the vas deferens were separated and then isolated and ligated. The Denonvilliers' fascia and the posterior fascia of the prostate were then dissected posterolaterally and the dissection continued to the apex of the prostate. To ensure nerve preservation during this process, it is important to avoid excessive instrument pressure to preserve the neurovascular bundle; dissection was also performed using a clip or Hem-o-lok.

During the lateral dissection, the intrafascial plane was exfoliated along the contour of the prostate. In the extrafascial plane, the levator ani muscle was used as a landmark. After that, the bladder neck and the prostate base were sufficiently separated, and the bladder neck was incised at the 6 o'clock position.

After dissection of the bladder neck, the anterior surface of the prostate was separated from the bladder. Minimal dissection of the bladder was achieved, and the Santorini plexus was preserved. Dissection continued through the anterior prostate to the prostate apex. An incision was made between the prostate apex and the distal urethra. Finally, the dissected specimen was placed in a specimen bag. Pelvic lymphadenectomy was considered and performed in patients with a high risk of BCR.

The vesicourethral anastomosis was started in the opposite direction to the traditional approach. From the 12 o'clock position of the bladder neck and urethra, two V-Loc sutures were placed as continuous sutures, one clockwise and the other counterclockwise. A new 18-Fr two-way Foley catheter was then inserted and filled with 150 cc of normal saline to check for leaks. After applying hemostatic material and positioning the drain, the peritoneal incision was closed using V-Loc suture material.

4. Statistical analysis

All statistics were obtained using SPSS version 29 (IBM Corp.). Independent sample *t*-test, chi-square test were used for continuous and categorical variables, respectively. A *p*-value of 0.05 or less was considered statistically significant.

Results

Table 1 shows the demographic and preoperative characteristics of 69 patients who underwent RARP and rsRARP, respectively since March 2019. The mean age of the patients was 66.5±6.4 and 67.3±7.5 years in RARP and rs RARP, and the mean initial PSA level was 10.7±8.0 and 8.9±5.8 ng/mL in RARP and rs RARP, respectively. There was no difference in the D'Amico risk group and Gleason score at biopsy between the two groups.

Postoperative and pathologic features are shown in Table 2. Console time was 184.8±47.6 minutes and 178.9±48.3 minutes in RARP and rs RARP, respectively (p=0.752). The EBL was 397±267 and 364±305 (p=0.820), and two and sev-

Table 1. Demographic and preoperative features

Variable	RARP (n=35)	rsRARP (n=34)	*p*-value
Age (yr), mean±SD	66.5±6.4	67.3±7.5	0.370
Initial PSA (ng/mL), mean±SD	10.7±8.0	8.9±5.8	0.105
D'Amico risk group, No. (%)			0.700
Low	11 (31.4)	9 (26.5)	
Intermediate	11 (31.4)	14 (41.1)	
High	13 (37.2)	11 (32.4)	
Gleason score biopsy, No. (%)			0.834
6	12 (34.3)	10 (29.4)	
7	13 (37.2)	15 (44.1)	
8-10	10 (28.5)	9 (26.5)	

RARP, robot-assisted radical prostatectomy; rsRARP, Retzius-sparing PARP; PSA, prostate-specific antigen.

Table 2. Postoperative and pathological features

Variable	RARP (n=35)	rsRARP (n=34)	*p*-value
Console time (min), mean±SD	184.8±47.6	178.9±48.3	0.752
Estimated blood loss (mL), mean±SD	397±267	364±305	0.820
Postoperative pT stage, No. (%)			0.067
T2	33 (94.1)	27 (79.4)	
T3	2 (5.9)	7 (20.6)	
Gleason score at surgery, No. (%)			0.408
6	7 (20.0)	4 (11.8)	
7	21 (60.0)	19 (55.8)	
8-10	7 (20.0)	11 (32.4)	
Clavien-Dindo complications, No. (%)			0.414
1-2	4 (11.4)	2 (5.9)	
3-5	0	0	
Postoperative continence (completely dry), No. (%)			
Immediate after catheter removal	2 (5.9)	25 (74.5)	<0.001
After 1 mo	12 (34.3)	25 (74.5)	0.002
After 3 mo	15 (42.9)	26 (76.5)	0.004
After 6 mo	22 (62.9)	30 (88.2)	0.014
After 12 mo	25 (71.4)	30 (88.2)	0.083
Positive surgical margin, overall, No. (%)	6 (17.1)	9 (26.5)	0.348
Potency at 12 mo (<65 yr), No. (%)	7 (53.8)	9 (64.3)	0.581
Biochemical recurrence at 1 yr, No. (%)	4 (11.4)	7 (20.6)	0.299

RARP, robot-assisted radical prostatectomy; rsRARP, Retzius-sparing RARP.

en patients were T3 or higher (p=0.067). There was no significant difference in Gleason score after surgery (p=0.408), and there were no patients with Clavien-Dindo grade 3 or higher (p=0.414). after surgery, urinary incontinence recovery at immediate, 1 month, 3 months, and 6 months (p<0.001, p=0.002, p=0.004, p=0.014) showed a significant difference between the two groups, but there were no differences at 12 months and PSM, potency, and postoperative BCR (p=0.083, p=0.348, p=0.581, p=0.299). Fig. 1 shows the change in the operating time from 279 to 87 minutes from the first case to the last case.

Discussion

Prostatectomy has made remarkable progress over the past few decades due to innovations in anatomy, techniques, and devices. Walsh and Donker [8] presented the relationship between neurovascular bundles and potency, while Costello et al. [9] investigated neurovascular bundles and cavernosal nerves; studies have also been performed on the recovery of many nerves around the prostate, overall erectile function, and incontinence. The detrusor apron and Aphrodite veil have also been identified [10,11]. Segmentation of approaches, such as those in the intra-, inter-, and extrafascial planes, have also aided in functional preservation and recovery [12,13]. In addition, the advent of precision instrumentation, such as laparoscopes and robotics, offers oncologic and functional outcomes comparable to those of the past with increased surgical convenience.

In 2010, Galfano et al. [5,14] presented a pure intrafascial approach called Retzius-sparing laparoscopic prostatectomy and reported on 200 surgical experiences. Lim et al. [6] demonstrated a statistically significant early recovery of continence through comparative studies using an anterior approach, and Dalela et al. [15] achieved the same with randomized controlled trial. The recovery of urinary continence after a follow-up of 12 months was also statistically significant in the meta-analysis by Checcucci et al. [16], whereas the PSM showed a low trend in the conventional technique. In addition, Nyarangi et al. [17] reported a surgical method that could be performed even in high-risk patients. Umari et al. [18], in a prospective comparative study

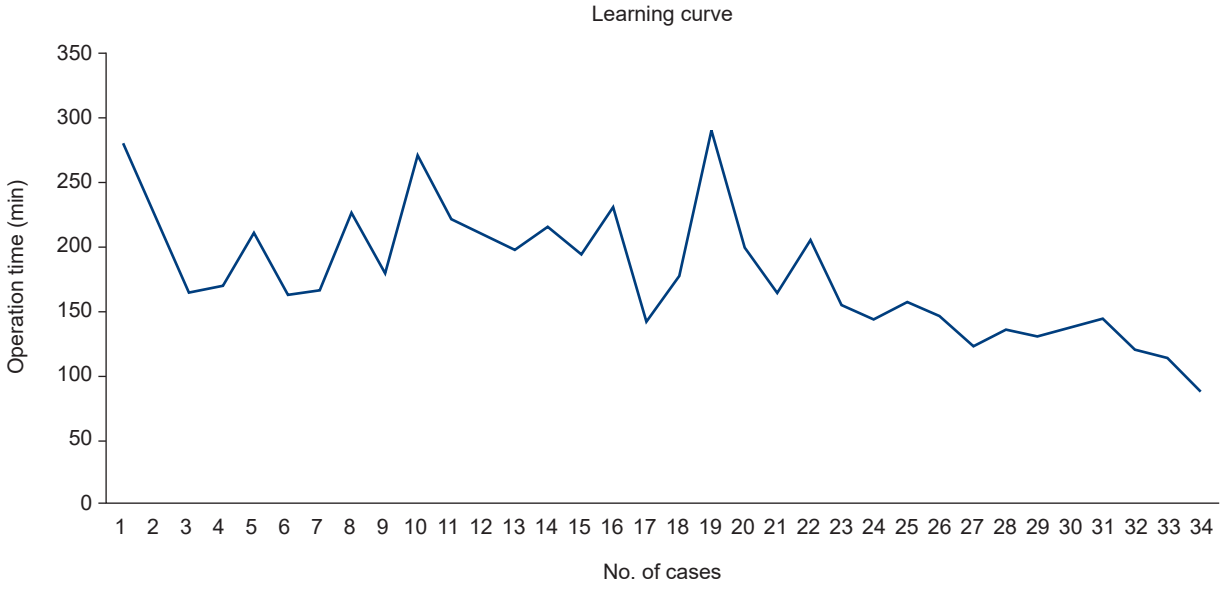

Fig. 1. Learning curve of Retzius-sparing robot-assisted radical prostatectomy.

of nearly 500 patients, showed that other indicators were similar and that quality of life was higher with faster recovery from urinary incontinence.

Interesting studies on learning curves have also been reported, Olivero et al. [19] divided clinicians into two groups: experienced surgeons and "learning curve" surgeons with no prior experience in robotic radical prostatectomy but more than 50 experiences in first-assist or robotic lymph node dissection. They found rsRARP to be a safe and feasible technique even for those who are new to robotic surgery.

The difference with this initial study is that a surgeon who had little experience with direct or indirect robotic prostatectomy, performed rsRARP surgery and compared it to the conventional method. The lack of experience with rsRARP is similar to that of many other hospitals. In addition, because rsRARP is a similar to the conventional method, it can be learned more quickly if the surgeon is familiar with RARP.

The results of this study were also compared with the earlier study by Galfano and the study by Olivero [14,19]. These studies are considered to be the beginning of rsRARP, so they can be used as a comparison. The operation time and oncologic and functional outcomes of early cases showed similar results to Galfano's study. In Olivero's learning curve study [19], the rsRARP operators had the advantage of sharing the experience of more than 50 surgical assistants and experienced operators such as Galfano. Galfano was one of the pioneers of the rsRARP procedure and is therefore an expert in this technique. The average operative time for learning curve surgeons was 179 minutes for the first 248 patients [19]. The operative time shown in this study was similar and gradually decreased as the patients were operated. The decrease in operative time as the number of cases increases in Fig. 1 is similar to the graph of the first 200 cases by Galfano, showing that this surgical method has good reproducibility [14].

Complications of Clavien-Dindo grade 3 or higher have not been reported, and it is believed that more surgical experience should be accumulated based on the incidence of complications reported by other authors. However, the absence of specific complications in these first 34 patients was a positive result in terms of the safety of the surgery. One patient who delayed conservative treatment experienced paralytic ileus and delayed catheter removal due to urine leakage on cystogram 1 week after surgery.

Early recovery of urinary continence, which has been demonstrated in several studies, was also evident in this study because rsRARP preserved multiple structures anterior to the prostate. Complete dryness was observed in 74.5% of patients immediately after catheter removal on postoperative day 7 and in 88% at 12 months. This finding

was similar to that of Lim et al. [6]. There are studies showing that there is no significant difference between the two surgical methods in the recovery of urinary continence at 12 months, and in this study the difference between the two groups decreased over time. However, the life satisfaction that urinary continence gives is not small [20].

In the case of rsRARP, PSM appeared relatively frequently in the early cases, but did not appear in the later 12 cases. In addition, it did not appear in the anterior portion. The slightly higher PSM in rsRARP in this study may be due to insufficient surgical skill in the early stage.

Since rsRARP separates the anterior part of the prostate in a similar way to the conventional basal and posterior parts, it can increase the possibility of PSM if there is cancer in the anterior part. Otherwise, surgical outcomes would be similar, as has been reported in recent studies showing similar results in PSM for each surgery [16]. Retzius-sparing surgery does not need to be performed if there is cancer in the anterior portion on preoperative examination. In addition, there is lymphatic tissue in the prostate anterior fat pad, and metastases are rarely found [21]. Therefore, prostatic fat pads should be carefully evaluated for lymph node metastasis prior to surgery and, if present, conventional surgical methods should be considered.

There are several limitations to this initial experience with rsRARP. First, RARP was performed by an experienced surgeon and rsRARP was performed by a surgeon who was performing robotic prostatectomy for the first time, so there may be a difference in skill between the two procedures that could lead to errors in interpreting which method is better. A large randomized controlled trial performed in multiple hospitals and by multiple surgeons is needed before this approach becomes more established. Second, functional outcomes such as continence and potency were also subjectively assessed in this study, which may have influenced our results. A measurable functional comparison between rsRARP and RARP would be more objective and interesting.

In conclusion, rsRARP is a highly reproducible procedure that even surgeons new to robotic prostate surgery can try. It is also a good surgical approach that shows oncologic results similar to the conventional approach with the advantage of early recovery of urinary incontinence.

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Comparison of transperitoneal and retroperitoneal robot partial nephrectomy for kidney tumors

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Background: Surgical techniques for small kidney tumors have been developed for decades, from open to robotic surgery. There are two approaches for partial nephrectomy: transperitoneal and retroperitoneal. We divided robotic partial nephrectomy cases into transperitoneal robotic partial nephrectomy (TRPN) and retroperitoneal robotic partial nephrectomy (RRPN) and compared the outcomes.
Methods: We retrospectively evaluated patients who underwent robotic partial nephrectomy at our hospital between November 2019 and May 2022. We reviewed patients' demographic and perioperative data.
Results: Seventy robotic partial nephrectomies were performed (35 TRPN and 35 RRPN). There were significant differences in operation time, estimated blood loss (EBL), tumor size, and the RENAL Nephrometry Score (RNS) between those who underwent TRPN and those who underwent RRPN. Larger tumors were noted in the TRPN group, and the RNS was higher. In contrast, the operation time was shorter, EBL was lower, and tumors were more likely to be located in the posterior and lower portions in the RRPN group than in the TRPN group.
Conclusions: In our study, RRPN had advantages over TRPN in terms of operation time and EBL. However, TRPN tended to be performed rather than RRPN for tumors that were more complex in terms of size or RNS. Although the choice between RRPN and TRPN depends on the surgeon's preference, RRPN seems effective for treating small kidney tumors if selected appropriately.

Keywords: Kdiney neoplasm; Nephrectomy; Robot surgery

Introduction

Radical nephrectomy has been the standard treatment for kidney cancer for decades since Robson et al. [1] introduced it as a treatment for renal cell carcinoma. Since then, partial nephrectomy, which is more nephron-sparing than radical nephrectomy, for small kidney tumors has been actively debated and considered non-inferior to radical nephrectomy in surgical outcomes, including overall survival and cancer-specific survival [2,3]. Although partial nephrectomy is mainly performed for clinical T1 tumors, it is also performed for clinical T2 tumors and has been increasingly performed for small kidney tumors because of the advantage of nephron preservation [4-6]. The surgical technique of partial nephrectomy has evolved in recent decades from open partial nephrectomy to laparoscopic and robotic partial nephrectomy [7,8].

Partial nephrectomy can be divided into the peritoneal or retroperitoneal approach [9]. The peritoneal approach has traditionally been practiced more than the retroperitoneal approach because of a wider surgical space and more familiar anatomical landmarks. Conversely, while the retro-

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peritoneal approach has a narrower surgical space, it allows direct access to the renal artery, and intraperitoneal organs such as the intestine, spleen, and liver can be avoided. Therefore, there is less pressure on intraperitoneal organ injury with the retroperitoneal approach, which is beneficial for restoring bowel function after surgery [10,11].

We conducted a retrospective study to compare transperitoneal robotic partial nephrectomy (TRPN) and retroperitoneal robotic partial nephrectomy (RRPN) performed by a single surgeon at our institution to investigate potential differences in tumor characteristics and surgical outcomes between the two procedures.

Methods

Ethical statements: This study was approved by the Institutional Review Board of Kosin University Gospel Hospital (IRB No. KUGH 2023-06-026) and was conducted in accordance with the recent Declaration of Helsinki. Informed consent was waived by the board.

We performed a retrospective evaluation using the electronic medical records of patients who underwent robotic partial nephrectomy from November 2019, when RRPN was first performed in our hospital, to May 2022. RRPN was performed by a single urologist (SHK).

We reviewed demographic and perioperative data, such as age, hospital stay, operation time (skin-to-skin), warm ischemic time (WIT), estimated blood loss (EBL) during surgery, positive surgical margin (PSM), tumor size, RENAL Nephrometry Score (RNS), tumor location, preoperative and postoperative estimated glomerular filtration rate (eGFR), and complications. Hospital stay was defined as the number of resource days from the day of surgery to the day of discharge. RNS was obtained with the method introduced by Kutikov and Uzzo in 2009 [12]. Complications were classified according to the Clavien-Dindo classification system [13]. Tumor location was assessed using computed tomography or magnetic resonance imaging and classified as upper/lower/unassessable and medial/lateral/unassessable. Preoperative eGFR was assessed within 1 month before surgery, and postoperative eGFR was assessed within 1 week before discharge. To assess postoperative eGFR change, we defined eGFR change as the postoperative eGFR value minus the preoperative value.

Statistical analysis was conducted with IBM SPSS. Mann-Whitney *U* test was used for quantitative variables, and the chi-square test for categorical variables. A significant *p*-value was determined as less than 0.05.

Results

Seventy robotic partial nephrectomies (35 TRPN and 35 RRPN) were performed. All surgeries were carried out using the da Vinci Xi system (Intuitive Surgical).

The median hospital stays after surgery (both TRPN and RRPN) was 8.38 days, operation time 148 minutes, WIT 27.26 minutes, EBL 278 mL, tumor size 2.37 cm, RNS score 5.89, eGFR change (postoperative eGFR–preoperative eGFR) –1.11. The two groups had statistically significant differences in operation time, EBL, tumor size, and RNS. However, no significant difference in age, length of hospital stays, WIT, PSM rate, eGFR changes, and complication rates was detected between the groups. Larger tumors were noted in the TRPN group, and the RNS was higher. In contrast, the operation time was shorter and EBL was lower in the RRPN group. In the RRPN group, the tumor tended to be significantly more posterior and lower, but the PSM and complication rates were not significantly different (Table 1).

There were two cases of PSM in the TRPN group and two cases in the RRPN group, but only one case of clear cell renal cell carcinoma in the TRPN group was confirmed as an angiomyolipoma by histopathological examination. There were no Clavien-Dindo grade 3 or higher complications in the TRPN group and three cases (urine leakage at the surgical site) in the RRPN group. Ureteral stenting or percutaneous nephrostomy was performed for the three cases.

Discussion

TRPN requires more dissection than RRPN, particularly when the tumor is located in the posterior portion. This difference in dissection may result in a shorter operation time (128±39 minutes vs. 169±51 minutes, $p<0.001$) and less EBL (136±164 mL vs. 420±641 mL, $p=0.015$) for RRPN. However, if the tumor is located in the anterior or superior portion, using the RRPN approach is difficult. This is why a significantly higher proportion of tumors in the posterior or inferior segments was noted in the RRPN group compared to the TRPN group. In addition, the narrower surgical

Table 1. Clinical characteristics and results of the TRPN and RRPN groups

Characteristic	TRPN	RRPN	Overall	*p*-value
Age (yr)	57.46±12.65	63.37±12.46	60.41±12.81	0.053
Hospital stays after surgery (day)	7.54±0.98	9.23±6.64	8.38±4.79	0.073
Operation time (min)	169±51	128±39	148±50	<0.001
Warm ischemic time (min)	29.56±7.76	25.29±5.73	27.26±6.99	0.056
Off clamp	17 (48.57)	14 (40.00)	31 (44.29)	0.47
Estimated blood loss (mL)	420±641	136±164	278±485	0.015
Positive surgical margin	2 (5.71)	2 (5.71)	4 (5.71)	1.000
Tumor size (cm)	2.77±1.54	1.96±0.91	2.37±1.32	0.01
RENAL Nephrometry Score	6.34±1.53	5.43±1.77	5.89±1.71	0.024
Location				
Anterior or posterior				<0.001
Anterior	15 (42.86)	5 (14.29)	20 (28.57)	
Posterior	8 (22.86)	24 (68.57)	32 (45.71)	
Non-assessable	12 (32.29)	6 (17.14)	18 (25.71)	
Upper or lower				0.031
Upper	14 (40.00)	5 (14.29)	19 (27.14)	
Lower	17 (48.57)	22 (62.86)	39 (55.71)	
Non-assessable	4 (11.43)	8 (22.86)	12 (17.14)	
Preoperative eGFR (mL/min/1.73 m^2)	95.00±21.92	88.91±24.26	91.96±23.16	0.275
Postoperative eGFR (mL/min/1.73 m^2)	90.00±26.55	91.69±21.34	90.84±23.92	0.771
eGFR change (mL/min/1.73 m^2)	−5.00±19.33	2.77±14.05	−1.11±17.22	0.059
Complications	1 (2.86)	5 (14.29)	6 (8.57)	0.198
Clavien-Dindo grade I	1 (2.86)	0	1 (1.43)	1.000
Clavien-Dindo grade II	0	2 (5.71)	2 (2.86)	0.493
Clavien-Dindo grade III	0	3 (8.57)	3 (4.29)	0.239

Values are presented as mean±standard deviation or number (%).
TRPN, transperitoneal robotic partial nephrectomy; RRPN, retroperitoneal robotic partial nephrectomy; eGFR, estimated glomerular filtration rate.

space in RRPN compared to TRPN tended to favor smaller tumors (2.77±1.54 cm vs. 1.96±0.91 cm, p=0.01). The results of our study are similar to those of other studies. Choi et al. [14] compared TRPN and RRPN conducted by a single surgeon. According to these authors, although there was no significant difference in tumor complexity or location between the two groups, the RRPN group had better results in terms of operation time (273 minutes vs. 244 minutes, p<0.001), WIT (21 minutes vs. 19 minutes, p=0.008), and EBL (150 mL vs. 100 mL, p=0.003). In Harke et al.'s multicenter analysis [15], the RRPN group had a shorter median operation time than the TRPN group after propensity score matching (139 minutes vs. 119 minutes, p<0.001), which included tumor characteristics and shorter hospitalization (9 days vs. 8 days, p<0.001). Zhou et al.'s meta-analysis of 21 studies [16] also showed significant benefits of RRPN in terms of operation time, length of hospitalization, and EBL. Although the studies had some variations, overall, RRPN outperformed TRPN in operative time and EBL. The RRPN group displayed a shorter operation time, consistent with prior research [14-16]. However, tumor size and RNS were greater in the TRPN group in our study. Thus, caution must be exercised when interpreting these results, as these variables may affect operation time. The EBL was also higher in the TRPN group, similar to other studies [14-16]. This finding could also be attributed to tumor complexity, such as tumor size and RNS.

Our study has some limitations. The study was a retrospective analysis, and patients were divided into two groups based on the surgical method used in their case. The decision regarding surgical method was influenced by the size and location of the tumor, which led to variations in tumor size, tumor complexity as measured by RNS, and tumor location between the groups. Conducting a retrospective comparison of the two surgical methods under similar conditions is infeasible because of the impact of tumor size and

location on the choice of surgical procedure. A large-scale randomized prospective study in which tumor size or location is matched between the study groups would elucidate the advantages and disadvantages of the two surgical techniques based on tumor location and complexity.

In our study, RRPN had advantages over TRPN in terms of operation time and EBL. RRPN is usually performed for renal masses in the posterior or lower portions. However, there is a tendency to perform TRPN rather than RRPN for tumors that are more complex in terms of size or RNS. Although the choice between RRPN and TRPN depends on the surgeon's preference, RRPN seems effective for treating small kidney tumors if selected appropriately.

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The effectiveness of Moodle's "Lesson" feature in pre-learning about arterial puncture and blood transfusion procedures

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Background: This study evaluated the effectiveness of Moodle's "Lesson" feature as a pre-learning tool for clinical skills among medical students.

Methods: The performance of 69 fourth-year medical students during practical sessions on arterial puncture and blood transfusion was assessed. These students engaged in pre-learning activities via Moodle's "Lesson" feature. We analyzed the survey results to gauge students' satisfaction and perceived usefulness of the pre-learning approach. Additionally, we compared the performance of the 2023 cohort, which took part in the pre-learning process, with students from 2020 to 2022 who did not have this preparatory component.

Results: Among the students surveyed, data from 59 respondents were analyzed. Satisfaction with the pre-learning segment was high, with a mean satisfaction score of 4.69 (standard deviation [SD]=0.62) and Cronbach's alpha of 0.918. The tool's perceived usefulness was also rated highly, with a mean score of 4.77 (SD=0.53) and Cronbach's alpha of 0.956. Students who used the pre-learning tool had a mean score of 84.20 (SD=14.74), whereas those who did not use the tool scored slightly lower, with a mean of 80.40 (SD=13.07); however, this difference was not statistically significant (p=0.196). Nonetheless, the 2023 cohort scores were generally higher across the various percentile measures than those of the 2020–2022 groups.

Conclusions: The pre-learning tool using the "Lesson" feature on Moodle proved useful and satisfactory for students learning clinical procedures. Further research with larger cohorts is required to validate these findings.

Keywords: Clinical skills; Lesson; Moodle; Pre-learning; Prior knowledge

Introduction

When teaching procedural skills, educators can use the nine instructional events outlined by Gagne to facilitate learning [1]. This framework is grounded in the information processing perspective, which examines the cognitive processes triggered in adults when exposed to different stimuli. The third stage involves prompting the recollection of prior learning, allowing students to link new data with existing knowledge [2].

From the perspective of cognitive load theory, which classifies cognitive load into three primary categories (in-

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trinsic, extraneous, and germane), a learner's preexisting knowledge plays a significant role in influencing the intrinsic load, which is determined by both the complexity of the content and the learner's background knowledge [3]. For effective learning, it is crucial to have well-structured educational content to ensure a reduction in extraneous load through clear and streamlined presentations, while also maximizing the germane load, leading to better knowledge retention and application [4].

While self-directed learning may offer numerous benefits over traditional teaching for aspiring healthcare professionals, it is essential that educators act as guides, ensuring that learners meet their deadlines [5]. From this perspective, a well-designed course on procedural skills should offer tailored guidance to students [6]. In essence, it is beneficial to provide students with a tool that provides guidance based on their academic level or previous knowledge before they begin to practice.

At the authors' institution, students voluntarily practice arterial puncture and blood transfusion techniques using diverse resources in an objective structured clinical examination (OSCE) practice room, either alone or in groups. They gather pertinent resources and refine their proficiency through self-directed learning. The authors crafted a structured pre-practice activity using the "Lesson" feature using Moodle version 3.0 software (Martin Dougiamas, Perth, Australia; http://www.moodle.org/) to guide their initial learning. This study sought to evaluate the effectiveness of this preparatory activity by examining survey responses and comparing the proficiency of students in arterial puncture and blood transfusion procedures with that of prior students using this structured approach. The goal of this evaluation is to ascertain the value of the pre-learning method incorporated with the "Lesson" tool on Moodle.

Methods

1. Research subjects

This study used data from 69 fourth-year medical students who had undergone practical arterial puncture and blood transfusion sessions between 2020 and 2023. We analyzed students' procedural performance assessments from 2020 to 2023 and delved into the learning activities of the 2023 cohort. To assess the effectiveness of pre-learning activities using the "Lesson" feature on Moodle, we looked at performance results spanning 3 years, from 2020 to 2022. This approach aims to minimize yearly variations in evaluations based on traditional methods and enhance the reliability of the study. We then compared these results with the performance evaluations of the new 2023 system. From 2020 to 2022, the pre-learning process was not incorporated into conventional procedural practice. In 2023, it was introduced to help students acquire prior knowledge of arterial puncture and blood transfusion procedures.

2. Applying the Lesson module for interactive learning in clinical procedures

In 2023, 69 fourth-year medical students participated in this study to assess newly introduced pre-learning sessions for prior knowledge acquisition. Students were tasked with completing activities on a web-based instruction (WBI) website for the first 3 days of their practice class, which was developed using the Moodle platform at the authors' institution. Students were informed that the pre-learning session would not be included in the final assessment results, and that they were required to complete the pre-learning course to proceed to the next procedural practice activity. The Moodle system automatically controlled the completion of the pre-learning sessions. We anticipated that by undergoing the pre-learning process, students would gain prior knowledge of arterial puncture and blood transfusion procedures.

For the pre-learning activity, we adopted the "Lesson" feature on Moodle platform [7]. This feature presents students with a series of HTML pages, each prompting them to make decisions based on the provided content. Depending on their choices, the students were guided to specific pages within the lesson, as shown in Fig. 1. This interactive tool not only generates personalized feedback and responses from instructors based on each student's decisions but also directs them through various sections of the lesson. By employing this approach, we enabled students to embark on customized learning journeys along predefined paths. Moreover, the module's ability to guide students is a key strategy for fostering self-directed learning.

For the lesson on arterial puncture and blood transfusion procedures, we incorporated 14 questions and 11 content pages as well as an essay component. The content covered in the lesson was derived from the standard teaching points established previously in regular lessons. We divided the

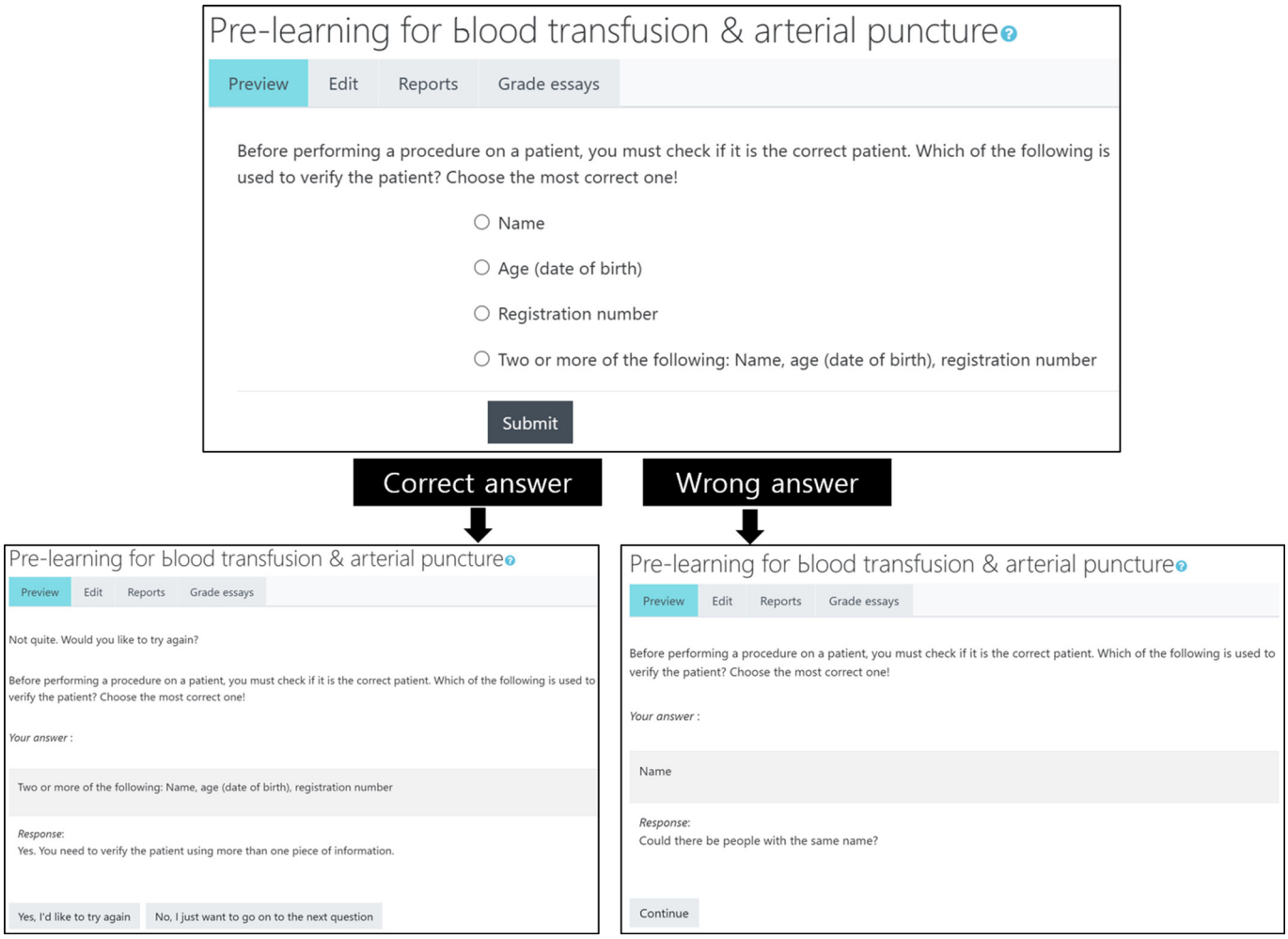

Fig. 1. Flowchart illustrating the pre-learning process for arterial puncture and blood transfusion procedures. Students followed the procedure outlined in the web-based instructional system. They engaged in a pre-learning activity using the "Lesson" feature on the Moodle platform. Here, students responded to questions, and subsequent instructions were tailored based on their answers.

learning process into two clusters to specifically address pleural procedures. The content pages set up a virtual clinical scenario before asking questions related to the procedure. After completing the procedural portion of the lesson, students were provided with explanations of the concepts and knowledge. The essay question was designed to allow students to reflect on and hypothesize the rationale behind certain steps in the procedural process. During the pre-learning phase, as students gained insight into the clinical skills they would be practicing, we provided feedback on their questions related to arterial puncture and blood transfusion procedures. For this purpose, we employed the "Forum" function on the Moodle platform. The "Forum" feature in Moodle is an effective and flexible tool for communication, and is specifically crafted to support interactive learning and discussion [7]. It allows users to post messages and structure conversations on a range of topics, fostering meaningful engagement between students and teachers through targeted discussions.

To bridge the gap between prior knowledge and practical skills, the students were instructed to voluntarily practice arterial puncture and blood transfusion procedures in an OSCE room during this period. This approach was aimed at offering students a hands-on learning experience that would improve their mastery and memory of these essential clinical procedures.

3. Assessments

After completing their pre-learning process on the WBI, the students were assessed by an instructor to evaluate their performance and provide feedback. On the fourth day of practice, instructors evaluated their procedural skills. The instructor provided feedback to each student in each class to ensure consistency and avoid any potential bias from varying teaching styles. Before starting, students logged into the Moodle app on their smartphones and accessed the assessment quiz. They then handed their devices to the instructor, who completed the evaluation. The instructor observed the students performing the arterial puncture and blood transfusion procedures. The quiz was concealed by a passcode. The instructor unlocked the quiz using the code and rated the students based on their observed skills. Feedback was shared through a smartphone application [8], and brief comments were provided immediately after the students practiced their procedures [9].

The assessment consisted of 36 items that addressed the essential criteria for effective arterial puncture and blood transfusion procedures. The items had graded responses that reflected students' proficiency levels. The instructor chose a response that represented the student's aptitude, which serves as the official assessment tool. Supplemental feedback could be provided if needed. After the evaluation, students reviewed the criteria and any immediate feedback provided by the instructor.

4. Survey

After completing the OSCE assessment, students were instructed to complete a "survey" presented on WBI about the pre-learning system provided for arterial puncture and blood transfusion procedures. We analyzed the survey results from the last session of the practical course to assess students' perspectives on the satisfaction and usefulness of the pre-learning process they engaged in for the first 3 days. The questionnaire consisted of 15 items. The initial seven items measured satisfaction levels, whereas the remaining eight evaluated the perceived usefulness of the educational system. Students indicated their agreement with each statement using a 5-point Likert scale, where 1 represented strongly disagree, 2 was disagree, 3 stood for neither agree nor disagree, 4 meant agree, and 5 denoted strongly agree [10].

5. Comparative analysis of arterial puncture and blood transfusion procedure assessment outcomes with prior results

We evaluated the performance of students in 2023 who underwent the recently implemented pre-learning process against that of students from 2020 to 2022 who practiced and were assessed without such a process. For comparison, we calculated the mean score and standard deviation (SD) from the 2023 assessment results, and determined the mean score (SD) using the combined data from 2020 to 2022.

6. Statistical analysis

After gathering feedback on the courses related to arterial puncture and blood transfusion procedures, Cronbach's alpha was used to assess the reliability of the survey items. We determined the mean and SD of the student answers for each question. To compare the performance outcomes of the procedures between 2020–2022 and 2023, we employed the independent *t*-test and the Mann-Whitney *U* test to compare the mean scores of both groups. All statistical analyses were performed using SPSS version 26 (IBM Corp.). Statistical significance was set at $p<0.05$.

Results

1. Assessment of the students' pre-learning activity

A total of 69 students were evaluated, with a mean score of 74.84 and an SD of 10.57. The scores ranged from a minimum of 38.90 to a maximum of 90.30 (Fig. 2). When the 69 students were split into two groups, the 18 students who took the arterial puncture and blood transfusion examinations and the 51 who did not, the mean scores (SD) of the procedural assessments were 75.38 (10.10) and 74.65 (10.82), respectively. No significant difference existed in the mean values between the two groups ($p=0.802$).

2. Satisfaction and usefulness of the pre-learning process for arterial puncture and blood transfusion procedures

Of the 69 students surveyed regarding the pre-learning segment utilizing the "Lesson" feature within the WBI system, 92.8% (n=64) responded. Valid data were extracted from 59 respondents, accounting for 85.5% of the total sample. The mean satisfaction score was reported at 4.69 with an SD of 0.62 (Table 1). For perceived usefulness, the mean score

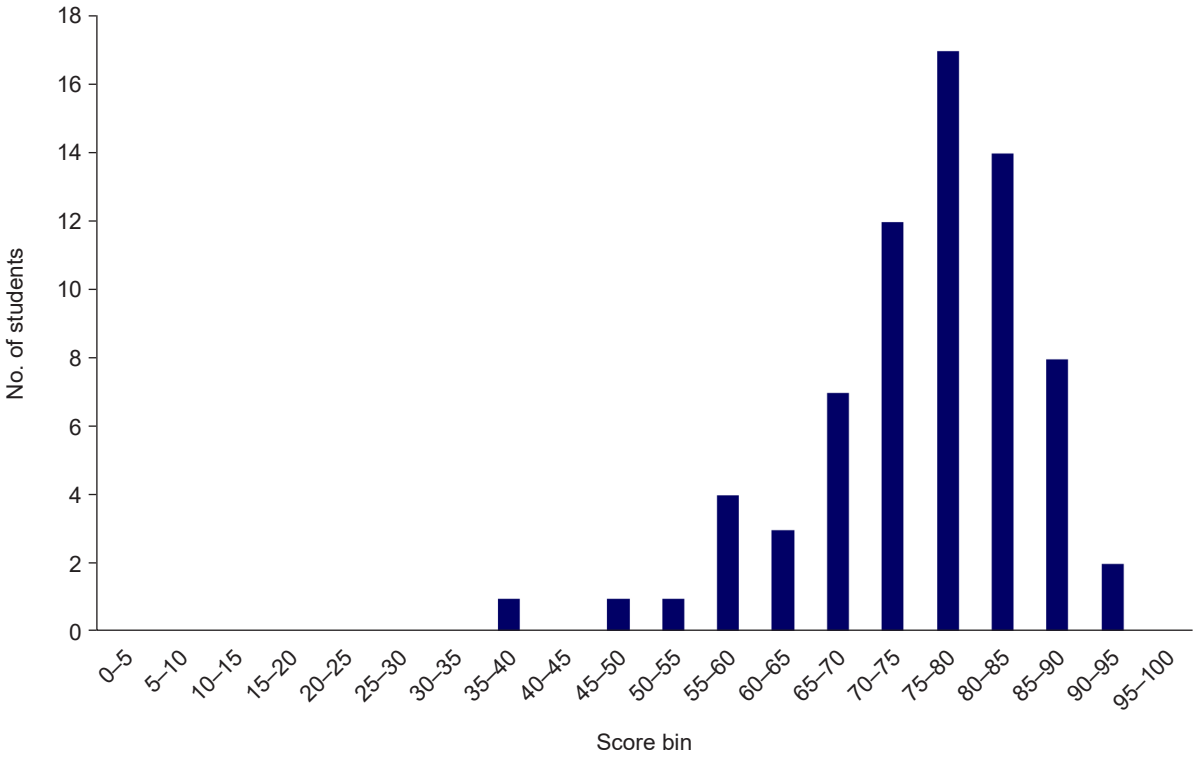

Fig. 2. Frequency distribution of student scores on the procedural assessment. In total, 69 students' scores were plotted with a bin width of 5.

Table 1. Degree of satisfaction with the pre-learning segment using the "Lesson" feature in the WBI system

Question	Min	Max	Mean	SD	Cronbach's α if item deleted	Cronbach's α (*p*-value)
1. I enjoyed the arterial blood puncture and blood transfusion procedure.	2	5	4.64	0.69	0.902	0.918 (*p*<0.001)
2. The teacher was adequately prepared to teach the procedure.	3	5	4.85	0.45	0.908	
3. I received adequate information for the procedure practice through the "pre-learning" process for arterial blood puncture and blood transfusion.	3	5	4.69	0.57	0.904	
4. The "pre-learning" process for arterial blood puncture and blood transfusion in the WBI system helped me acquire the skills.	3	5	4.73	0.55	0.899	
5. The "pre-learning" process for arterial blood puncture and blood transfusion in the WBI system was technically convenient and easy to learn.	2	5	4.54	0.82	0.923	
6. The "pre-learning" process for arterial blood puncture and blood transfusion was helpful for self-directed learning.	3	5	4.69	0.59	0.901	
7. Overall, I am satisfied with the "pre-learning" process during the arterial blood puncture and blood transfusion practice.	2	5	4.68	0.65	0.900	

WBI, web-based instruction; SD, standard deviation.

forum during the course indicates the course's thoughtful design and clarity.

Despite anticipation that the lesson course may be highly effective in this study, the mean assessment score during the practice period was not as elevated as expected, sitting at 74.84 with an SD of 10.57, which is considered the mean based on data from recent years. However, the 2023 cohort exhibited a trend toward higher scores in the collaborative

Table 2. Degree of usefulness of the pre-learning segment using the "Lesson" feature in the WBI system

Question	Min	Max	Mean	SD	Cronbach's α if item deleted	Cronbach's α (*p*-value)
1. The WBI "pre-learning" process for learning arterial blood puncture and blood transfusion was a useful tool for receiving the necessary information for actual practice.	3	5	4.75	0.54	0.944	0.956 (*p*<0.001)
2. The "pre-learning" process for arterial blood puncture and blood transfusion remains stored online even after the practice session has ended, so I can revisit and learn whenever necessary. This helps maintain procedural skills.	3	5	4.71	0.62	0.951	
3. The knowledge gained from the arterial puncture and blood transfusion "pre-learning" will be helpful when performing the procedure on actual patients.	3	5	4.76	0.54	0.947	
4. The "pre-learning" process for arterial blood puncture and blood transfusion using the WBI system is useful because there are no time and space constraints.	3	5	4.80	0.52	0.953	
5. I can repeat the arterial puncture and blood transfusion "pre-learning" process indefinitely, which helps with repetitive learning.	3	5	4.76	0.54	0.949	
6. The "pre-learning" process for arterial blood puncture and blood transfusion provided online can be accessed through smartphones, making it convenient to use during practice.	3	5	4.86	0.43	0.953	
7. There is an online space (forum) for feedback on the "pre-learning" process for arterial puncture and blood transfusion, making it useful as I can receive additional feedback when needed.	3	5	4.81	0.43	0.949	
8. If a "pre-learning" process is provided for other procedural practices, it will be helpful for learning the procedure.	3	5	4.69	0.62	0.951	

WBI, web-based instruction; SD, standard deviation.

was 4.77 with an SD of 0.53 (Table 2). The internal consistencies, as measured by Cronbach's alpha, for the satisfaction and usefulness scales were 0.918 and 0.956, respectively, indicating high reliability. Overall, the students were satisfied with the pre-learning tool and found it beneficial to their learning.

3. Comparative analysis of arterial puncture and blood transfusion procedure examination outcomes with prior results

While 69 students completed the pre-learning process for arterial puncture and blood transfusion procedures, only 18 had the opportunity to undergo examination for these two procedures. This was because the items on the collaborative regional procedural examination were randomly assigned to the students who applied for the exam. In 2023, the performance of 18 students in conducting arterial puncture and blood transfusion was tested. The performance of 65 students for the same procedures between 2020 and 2022 were examined.

The mean score of students who completed the pre-learning segment before the assessment was 84.20 (SD=14.74).

Table 3. Descriptive statistics of examination scores: 2023 versus 2020–2022

	Group	
	2023	2020–2022
No. of participants	18	65
Examination score		
Minimum	60.34	37.60
25th percentile	69.83	73.68
Median	92.24	81.82
75th percentile	96.55	90.19
Maximum	100	100
Range	100–60.34	100–37.60
Mean±SD	84.20±14.74	80.40±13.07

p-value was calculated using the independent *t*-test (*p*=0.292) and using the Mann-Whitney *U* test (*p*=0.196).

In contrast, students who did not undergo the pre-learning process had a mean score of 80.40 (SD=13.07) (Table 3). The difference in scores was not statistically significant (F=2.081, *p*=0.292 for the independent *t*-test; *p*=0.196 for the Mann-Whitney *U* test), as shown in Fig. 3. However, the mean, 75% percentile, median, and minimum scores for the

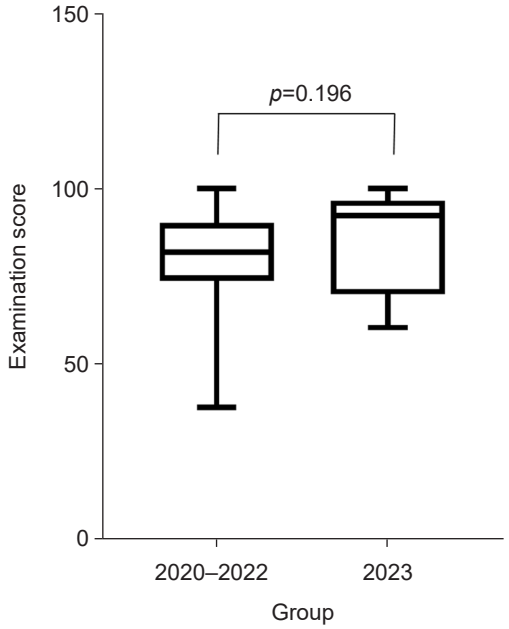

Fig. 3. Examination score distribution: 2023 versus 2020–2022. We employed parametric and non-parametric methods to compare the mean difference between the two groups due to the smaller sample size in the 2023 group. Consequently, we utilized the independent *t*-test as a parametric method and the Mann-Whitney *U* test as its non-parametric counterpart.

2023 group were higher than those for the 2020–2022 group.

Discussion

Various theories emphasize the critical role of prior knowledge in learning clinical skills. According to skill acquisition theory, students with existing relevant knowledge progress faster through the learning stages (cognitive, associative, and autonomous) [11,12]. They may skip the initial stages, that focus on basic concepts, and quickly move on to refining their skills. Constructivist learning theory suggests that learners build on existing knowledge to assimilate new information, enabling students with a strong knowledge base to integrate new skills more deeply and cohesively [13]. Schema theory posits that preexisting knowledge helps form schemas, which are conceptual frameworks that simplify the understanding of new information. In clinical skills, having a schema for a similar procedure facilitates the learning of new tasks by adapting existing schemas [14,15].

Students with prior knowledge typically show greater confidence and motivation to acquire new skills, which leads to more active engagement with educational materials [16,17]. Their solid foundation in relevant areas results in fewer mistakes during skill acquisition because they can anticipate and navigate challenges more effectively [18]. This extensive background is vital for clinical reasoning, which is a key component of clinical skill execution, and enhances their problem-solving abilities and decision-making during clinical procedures [19].

Given the vast amount of knowledge available in medical education, teaching strategies have shifted from simply imparting information to facilitating self-directed learning [20,21]. During the COVID-19 pandemic in particular, this paradigm shift in medical education became even more pronounced owing to the challenges of in-person instruction, emphasizing the need for self-directed learning [22].

With the advancements in online educational technology, educators now have a variety of tools to choose from to enhance student learning [23,24]. The “Lesson” feature in Moodle, which we utilized in this study, offers versatile functions and significantly enhances the effectiveness of self-directed learning. One of the most powerful features of a lesson is that educators can design a learning path tailored to students’ capabilities, such as their prior knowledge [7]. Despite being one of the world’s most popular learning platforms, Moodle often has a limited range of capabilities put to use, with features such as assignments, quizzes, and forums being most frequently employed by users [25]. This might stem from the fact that many educators, given their busy schedules, find it challenging to fully explore and utilize all of Moodle's features or adopt new teaching methods. Additionally, some of Moodle's features lack an intuitive design, complicating the content-creation process [26]. However, certain features such as “Lesson” have great potential for enhancing medical education.

We addressed a weakness in the lesson course by introducing a "Forum" section. The course module was designed to impart knowledge on arterial puncture and blood transfusion techniques. However, we acknowledge that students, due to their varying academic backgrounds, may encounter unresolved questions. To accommodate this, students could post outstanding issues or inquiries that were not addressed during the lessons. Instructors would provide responses to these queries in the forum section. The fact that we received only nine questions from the students via the

regional examination focused on arterial puncture and blood transfusion procedures (Table 3). Although this slight increase in scores for the 2023 cohort was not statistically significant compared to the other groups as shown in Fig. 3, it is still noteworthy for the purpose of improving academic performance.

When using Moodle's editing mode, educators can easily import questions, create new content pages, or add question pages to the lesson module [27]. By setting specific learning objectives for different sections of the lesson, instructors can organize the material into clusters. This organization facilitates the creation of a branched learning path, guiding students to the next relevant step in their study. The lesson includes a variety of multi-choice questions, content pages, and essay pages, all of which are interconnected to tailor the learning experience based on student responses. This approach enables the algorithm to provide personalized instruction that accommodates the diverse academic backgrounds of students. Nevertheless, extant literature on the use of Moodle's lesson modules is scant, with only a few studies exploring their application outside the field of medical education [28].

According to a survey evaluating student satisfaction and the usefulness of the prior learning component within the lesson module, students were reportedly fully satisfied with the course and their academic achievements were correspondingly high. As shown in Table 1, students assigned relatively lower scores to the question concerning the user-friendliness of the pre-learning process, with a mean (SD) of 4.54 (0.82). This may be attributed to the fact that while Moodle's lesson activity is relatively straightforward to use, it may lack advanced features that enhance user friendliness, probably because of technical limitations. Visually, it also falls short of other commercial programs, which could have influenced the survey's somewhat lower scores.

Despite these issues, students regarded the previous learning course that incorporated Moodle's "Lesson" features as more valuable. This positive perception appears to be linked to the recognition of the course's significant benefits, despite any technical shortcomings of Moodle with mean item means (SDs) of 4.77 (0.53) and 4.69 (0.62) for usefulness and student satisfaction, respectively.

We developed this prior-learning course using the lesson module in Moodle exclusively for the two clinical procedures, which limited its generalizability to other OSCE items. Additionally, we analyzed the postprocedural practice assessment results of 18 students who underwent arterial puncture and blood transfusion as part of the 2023 collaborative regional examination and compared them to those of 51 students assessed with different procedures. Despite finding no statistically significant differences between the two groups, the limited number of students tested with arterial puncture and blood transfusion procedures constrained the generalizability of our findings. Consequently, any conclusions drawn from these data should be considered with caution because of potential interpretative limitations. Although we used the mean values from the 2020 to 2022 cohorts for our analyses to mitigate the differences between groups, potential biases could still affect the results and their interpretation.

In conclusion, prior knowledge is an important factor for procedural clinical skill competency. From this standpoint, it is beneficial for students to gain knowledge before performing these skills. The lesson course, utilizing Moodle's "Lesson" features, provided satisfaction and was useful for students to acquire prior knowledge of arterial puncture and blood transfusion procedures. To extend the generalizability of Moodle's "Lesson" features to pre-learning clinical procedural skills, further research with a larger sample of student data is warranted.

Article information

Conflicts of interest

Hyunyong Hwang is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Author contributions

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Case report

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Perioperative cutaneous complications in an elderly patient due to inappropriate use of a forced-air warming device and underbody blanket: a case report

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Forced-air warming is commonly utilized to prevent perioperative hypothermia. Underbody warming blankets are often employed to secure a larger area for patient warming. While forced-air warming systems are generally regarded as safe, improper usage poses a risk of cutaneous complications. Additionally, the influence of underbody blankets on cutaneous complications remains uncertain. We present a case of cutaneous complications resulting from the improper utilization of a forced-air warming device and an underbody blanket. A 79-year-old man presented to the hospital for robotic proctectomy under general anesthesia. The surgery lasted for 7 hours, and the forced-air warming device with underbody blanket operated continuously for 5 hours intraoperatively. The surgery was completed without any incidents. However, first-degree burns on the patient's back, along with superficial decubitus ulcers on his right scapula, were observed after surgery. To prevent cutaneous complications, clinicians must adhere to the manufacturer's guidelines when utilizing a forced-air warming system. Compared to overbody blankets, underbody blankets have limitations in monitoring cutaneous responses. Ensuring patient safety requires selecting an appropriate blanket for scheduled operations.

Keywords: Case reports; Intraoperative complications; Intraoperative monitoring; Patient safety; Perioperative care

Introduction

Perioperative hypothermia is a common issue, which can lead to various complications such as cardiac abnormalities, impaired wound healing, increased surgical site infections, and coagulopathies [1]. To prevent perioperative hypothermia, a forced-air warming (FAW) system has been commonly utilized with the attachment of a warming blanket. Warming blankets are often used by covering patients, but they are sometimes placed underneath patients to secure sufficient skin warming, especially in surgeries with a wide surgical area such as abdominal surgery [2]. However, the effect of the underbody blanket on the patient's cutaneous complications is not clear. Additionally, although the FAW system is widely used as a safe device, there is a risk of burns or pressure ulcers, especially when used improperly [3,4]. We present a case of pressure ulcers and low-temperature burns in an elderly patient who underwent prolonged surgery under general anesthesia with an underbody warming blanket. Although cutaneous complications caused by the misuse of the FAW system are not novel discoveries, we consider our case report valuable due to its educational significance for other clinicians in terms of the proper utilization of the FAW system [5].

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Case

Ethical statements: This study was exempted from review by the Institutional Review Board of Inje University Busan Paik Hospital (IRB No: 2023-01-038). Informed consent was waived due to the retrospective study.

A 79-year-old man presented to the hospital for robotic proctectomy under general anesthesia. He had a history of rectal cancer and had undergone transarterial chemoembolization treatment for hepatic cellular carcinoma but was otherwise healthy. He was premedicated intramuscularly with 0.2 mg glycopyrrolate and 20 mg famotidine. Before he entered the operating room, an FAW blanket (Bair Hugger, Model 63500; Arizant Healthcare, Inc.) was placed on the surgical bed. After he lay on the surgical bed, the Bair Hugger warming device (Model 505; Arizant Healthcare, Inc.) was attached to the blanket to provide him warmth. In addition to the FAW system, a heating circuit system (Mega Acer kit; ACE Medical) was employed to maintain the patient's body temperature. Anesthesia was induced with propofol, lidocaine, and remifentanil, and rocuronium was injected to facilitate endotracheal tube insertion. Anesthesia was maintained with sevoflurane administration and continuous remifentanil and rocuronium infusion. For more precise monitoring of the patient's condition intraoperatively, a central venous catheter was inserted into the right internal jugular vein and an arterial catheter into the left radial artery. The patient's body temperature was measured using a Bair Hugger temperature monitoring sensor (Model 36000; Arizant Healthcare, Inc.) attached to his forehead. Thirty minutes after the surgery began, the patient's body temperature measured 36.3 °C (Fig. 1). The surgery lasted for 7 hours, and the patient maintained a lithotomy position for 1 hour, a lithotomy-Trendelenburg position (Fig. 2) for 5 hours and 30 minutes, and a supine position for 30 minutes. No complications occurred intraoperatively, and the patient's vital signs were within normal limits. The FAW device operated at a high temperature (43.0 °C), and both the FAW device and heating circuit system were turned off when his body temperature reached 37.8 °C, 5 hours after the surgery started. After surgery,

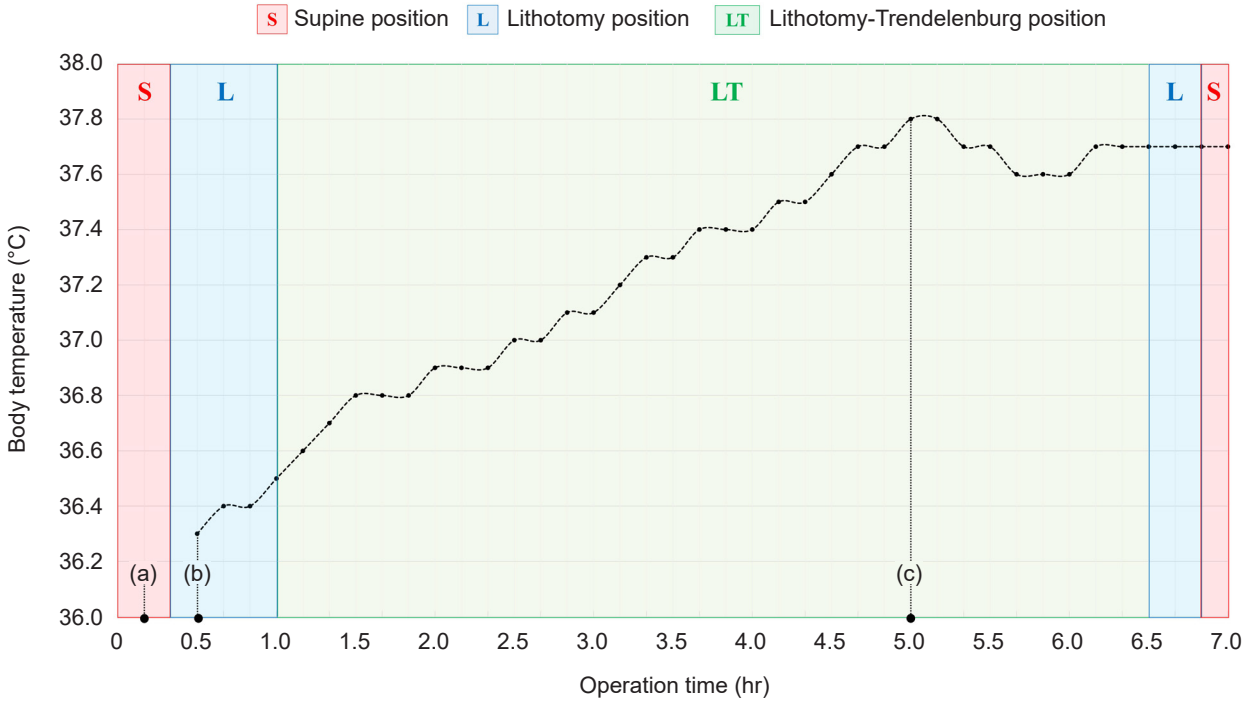

Fig. 1. Changes in body temperature and surgical position. (a) Start of induction of general anesthesia. (b) Start measuring body temperature. (c) Turning off the forced-air warming system. The changes in the patient's position during surgery are differentiated by boxes of different colors.

his body temperature was 37.7 °C. After tracheal extubation, he was transferred to the surgical intensive care unit. During the examination of the patient's skin in the surgical intensive care unit, his back skin was generally reddish. Large skin erosions at 10×5 and 5×8 cm on the right scapula (Fig. 3) and reddish linear skin lesions around the shoulder were observed (Fig. 4). He complained of an itching sensation on his back. The hospital dermatologist diagnosed the skin lesions as superficial decubitus ulcers and first-degree burns, which appeared to have resulted from prolonged exposure to warm air convected by underbody blanket. His skin was treated symptomatically, and he was transferred to a general ward on postoperative day 2. On postoperative day 12, he was discharged from the hospital without any observed complications.

Discussion

The FAW system maintains patients' body temperature by transferring heat through warm air convection and preventing heat loss from the areas covered by the blanket [6]. Due to this mechanism, the larger the area covered by the

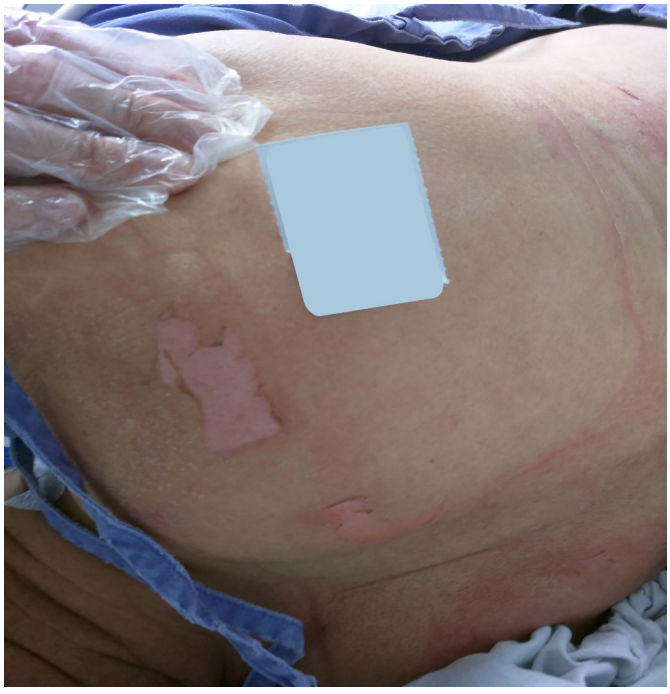

Fig. 3. Skin erosions on the right scapula. The areas of erosion measured 10×5 and 5×8 cm. The image has been altered to obscure any personal identifying information of the patient.

Fig. 2. Lithotomy-Trendelenburg position. Bilateral shoulder supports (black arrowheads) were used so that the patient would not slip from the bed intraoperatively.

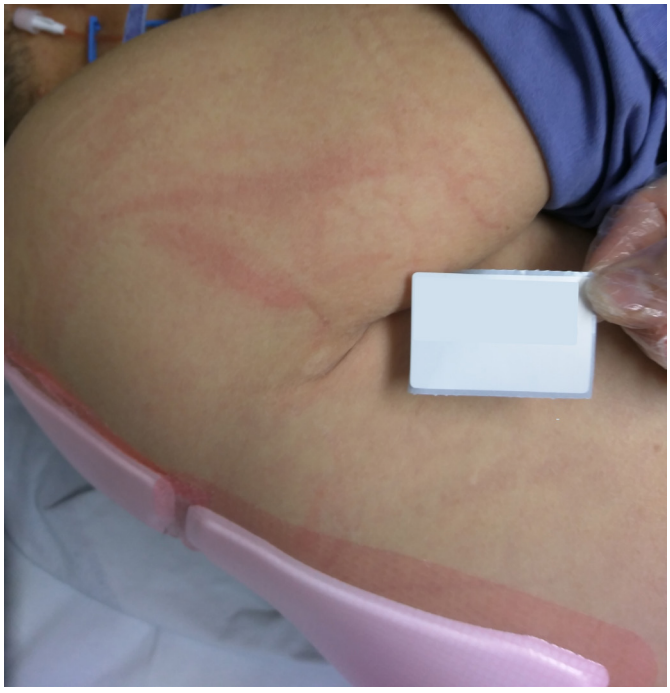

Fig. 4. Reddish linear skin lesions around the shoulder. The image has been altered to obscure any personal identifying information of the patient.

blanket, the greater the efficiency of the FAW system [7]. Along with surgical draping, the underbody blanket secures a larger body surface and enables sufficient warm air convection over the patient's body [2]. However, periodically assessing the patient's skin in contact with the underbody blanket during surgery poses a challenge. Additionally, the underbody blanket can experience limitations in expansion due to manipulation of the surgical bed, such as tilting, which can result in partial compression of the blanket against the patient. The restrictions in blanket expansion can force air into smaller areas, potentially increasing the risk of burns [8]. These facts suggest that the utilization of underbody blankets may impact the occurrence of perioperative cutaneous complications in patients. However, due to the lack of research on the relationship between underbody blankets and cutaneous complications, it is difficult to determine whether the utilization of underbody blankets increases the occurrence of perioperative cutaneous complications.

There are two hypotheses regarding the mechanism behind the development of skin lesions in our patient. The first hypothesis attributes the development of the pressure ulcer to a cascade of events initiated by a mild burn from prolonged heat exposure caused by the underbody blanket, subsequently compounded by pressure due to the surgical position. The epidermis, compromised by the mild burn, would have become vulnerable to pressure and friction, thus making the development of pressure ulcers more likely. The second hypothesis supposes that hyperthermia, independent of the occurrence of a burn, contributed to the development of the pressure ulcer. Pressure ulcers occur due to tissue ischemia and necrosis resulting from sustained and excessive external pressure [9]. As the body temperature increases, the metabolic rate and oxygen consumption of the tissue also increase [10]. The elevated metabolic rate and oxygen consumption of the tissue would worsen tissue necrosis, consequently leading to the development of pressure ulcers.

Since burns related to the utilization of the FAW system are rare when adhering to the manufacturer's guidelines, the majority of burn cases resulting from the use of the FAW system are a consequence of its misuse [4]. The most common misuse of the FAW system is "hosing," which involves using the FAW device without a blanket and can result in burns to patients, even with short-term use [4,11]. Brauer et al. [12] reported severe cutaneous complications in a patient using an underbody blanket, likely resulting from warming the lower extremities during aortic cross-clamping. This practice is contraindicated according to the manufacturer's guidelines. Although we used the FAW device with a blanket in non-cardiac surgery in this case, our adherence to the manufacturer's guidelines was deficient in several aspects.

Firstly, we did not adjust the air temperature or stop warming when the patient's body temperature was normalized, as outlined in the manufacturer's guidelines. The NICE (National Institute for Health and Care Excellence) guidelines recommend maintaining the patient's body temperature between 36.5 and 37.5 °C [13]. Adjusting the air temperature not only prevents hyperthermia but also reduces the rate of sweating for patients, leading to increased thermal comfort and satisfaction [14]. However, we did not focus on the patient and were negligent in monitoring vital signs. As a result, we only realized later on that the patient's body temperature had risen too high. We should have been monitoring the patient's body temperature regularly and considering adjusting the air temperature or halting the operation of the FAW system when the patient's body temperature was within the normal range.

We also failed to properly monitor our patient's cutaneous response, which is crucial for preventing complications. The manufacturer's guidelines recommend checking every 10 to 20 minutes when the FAW system is used for non-communicative individuals. It was challenging to closely examine the cutaneous response of a patient surrounded by an underbody blanket and surgical draping during surgery. Despite the difficulty, we acknowledge our lapse in monitoring. With more vigilant observation, we could have identified cutaneous complications earlier, enabling faster intervention.

Finally, the underbody blanket we utilized, Bair Hugger (Model 63500), is recommended for supine, prone, and lateral positions, but not for steep Trendelenburg position in robot-assisted surgery. While the product manual does not explicitly prohibit the use in the Trendelenburg position, there is currently no research indicating the safety of using it in this position. Therefore, opting for a blanket recommended for use even in the Trendelenburg position, such as an overbody blanket, appears to be safer for the patient.

To prevent cutaneous complications, clinicians must

utilize the FAW system following the manufacturer's guidelines. During surgery, anesthesiologists should continuously monitor vital signs and periodically evaluate patients' cutaneous responses to the utilization of the FAW system. While the underbody blanket effectively prevents hypothermia, there is a potential for it to have a negative impact on the occurrence of cutaneous complications. To ensure patient safety, an appropriate blanket should be chosen for the scheduled surgery.

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Case report

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Selective adjuvant radiation therapy for distant lymph node metastasis in patients with stage 4B epithelial ovarian cancer: a case series

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Although the efficacy of surgery followed by taxane- and platinum-based systemic chemotherapy has been clearly demonstrated in the standard first-line treatment of epithelial ovarian cancer, the role of radiation therapy for distant lymph node metastasis in patients with epithelial ovarian cancer is not well-established due to a lack of reported studies. We identified four patients who underwent selective adjuvant radiation therapy for neck and para-aortic lymph node lesions after primary debulking surgery between 2020 and 2022, followed by platinum-based chemotherapy for stage 4B high-grade serous ovarian cancer. Through a retrospective review of medical records, we analyzed patient clinicopathologic features, treatment course, and imaging findings. The median age was 49.25 years (range, 46–54 years). All patients had the International Federation of Gynecology and Obstetrics stage 4B disease. Following primary debulking surgery, all patients received weekly paclitaxel-carboplatin chemotherapy and maintenance treatment with poly(ADP-ribose) polymerase (PARP) inhibitors. All patients received selective adjuvant radiation therapy for neck and para-aortic lymph node metastasis before PARP inhibitor maintenance. The median follow-up time was 36.75 months (range, 19–45 months). All patients achieved a complete response. None of the patients experienced disease recurrence or died during the follow-up period. The management of distant lymph node metastasis in patients with epithelial ovarian cancer remains a matter of debate. Selective adjuvant radiation therapy in first-line treatment for ovarian cancer appears to be a feasible approach with maintenance therapy for stage 4B epithelial ovarian cancer.

Keywords: Adjuvant radiotherapy; Case reports; Lymphatic metastasis; Ovarian neoplasms; Poly(ADP-ribose) polymerase inhibitors

Introduction

Standard first-line treatment for epithelial ovarian cancer (EOC) consists of primary debulking surgery (PDS), adjuvant platinum-based combination chemotherapy, and individualized maintenance approaches [1]. PDS plays a key role in the treatment of EOC. Maximal cytoreduction was one of the most reliable indicators of survival outcomes among patients with stage III or stage IV ovarian cancer in a meta-analysis [2].

Recent research from a randomized controlled trial (the LION study) found that systematic lymphadenectomy was

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not beneficial for patients with advanced EOC with clinically negative lymph nodes who underwent macroscopically complete resection [3]. However, other studies have reported potential survival advantages of retroperitoneal lymphadenectomy for patients with advanced high-grade serous carcinoma (HGSC) after macroscopically complete tumor resection [4]. The lymphadenectomy group in the LION study indicated that systematic lymphadenectomy was associated with a substantial increase in morbidity. In addition, distal lymph node metastasis resection of advanced ovarian cancer requires additional surgical time.

The effectiveness of radiation therapy in treating distant lymph node metastases from other gynecologic malignancies has been thoroughly evaluated [5,6]. In EOC, it remains unclear whether radiation therapy to metastatic distant lymph nodes contributes to subsequent increases in the survival rate. We retrospectively reviewed four HGSC patients who underwent adjuvant radiation therapy after PDS and platinum-based combination chemotherapy to determine a feasible approach for distant lymph node metastasis in EOC.

Case

Ethical statements: The Institutional Review Board of Kosin University Gospel Hospital reviewed and approved this report (No 2023-10-002). Informed consent was waived.

1. General information

Between January 2020 and February 2022, we identified four patients diagnosed with HGSC who underwent selective adjuvant radiation therapy at neck and para-aortic lymph node lesions after PDS followed by platinum-based chemotherapy (weekly paclitaxel and tri-weekly carboplatin). PDS was performed by a single gynecologic oncologist. The extent of the surgery included bilateral salpingo-oophorectomy, hysterectomy, omentectomy, bilateral pelvic lymph node dissection, and removal of any visible tumors from the pelvic and low abdominal areas. Except for the subclavian lymph nodes and the para-aortic lymph nodes located above the level of the inferior mesenteric artery, the patients underwent maximal cytoreduction surgery (residual tumor of <1 cm). The para-aortic lymph node lesion firmly attached to the major vessels, such as the aorta and vena cava, was considered inoperable. In such cases, we performed a biopsy of the lateral lesion through maximal effort of cytoreduction. Blood Sanger sequencing was immediately performed after diagnosis by histology. The patients' clinical aspects and imaging findings were analyzed retrospectively by assessing their medical records. Clinical details, age at diagnosis, the International Federation of Gynecology and Obstetrics (FIGO) stage, histology, preoperative tumor markers, operative findings, adjuvant treatment, status of *BRCA* mutation, follow-up duration, and current status were reviewed.

2. Radiation therapy method

All patients underwent positron emission tomography-computed tomography (PET-CT) before surgery, and fine needle aspiration biopsy confirmed that the PET-CT showed a supraclavicular lymph node (Fig. 1). Based on the results of the BRCA test, poly(ADP-ribose) polymerase (PARP) inhibitor maintenance was performed after standard treatment of PDS and platinum-based combination chemotherapy. All patients were in complete remission (CR) with no evidence of disease at the beginning of maintenance treatment. Based on the preoperative CT scan, it was determined that radiotherapy would be appropriate for lymph node lesions that exceeded a size of 1 cm and were localized within a limited anatomical region. Conversely, lymph node lesions exhibiting both nodular and diffuse characteristics were decided beyond the scope of radiotherapy, as it was determined that chemotherapy had already covered the lesion within the therapeutic range. This evaluation was conducted by a multidisciplinary team that included a gynecologic oncology radiologist before radiation therapy. Before maintaining the PARP inhibitor, the multidisciplinary team determined the optimal timing for selective adjuvant radiation therapy for the distant metastatic lymph node, which encompassed para-aortic and subclavian lymph node lesions on PET-CT. CT-based three-dimensional treatment planning was performed for all patients. The clinical target volume of radiation therapy was tailored for each patient. For either supraclavicular lymph node or para-aortic lymph node metastasis, the entire lymph node lesion was designated as the clinical target volume. The total radiation dose was 50.4 Gy and was delivered in 28 fractions of 1.8 Gy to each lymph node area.

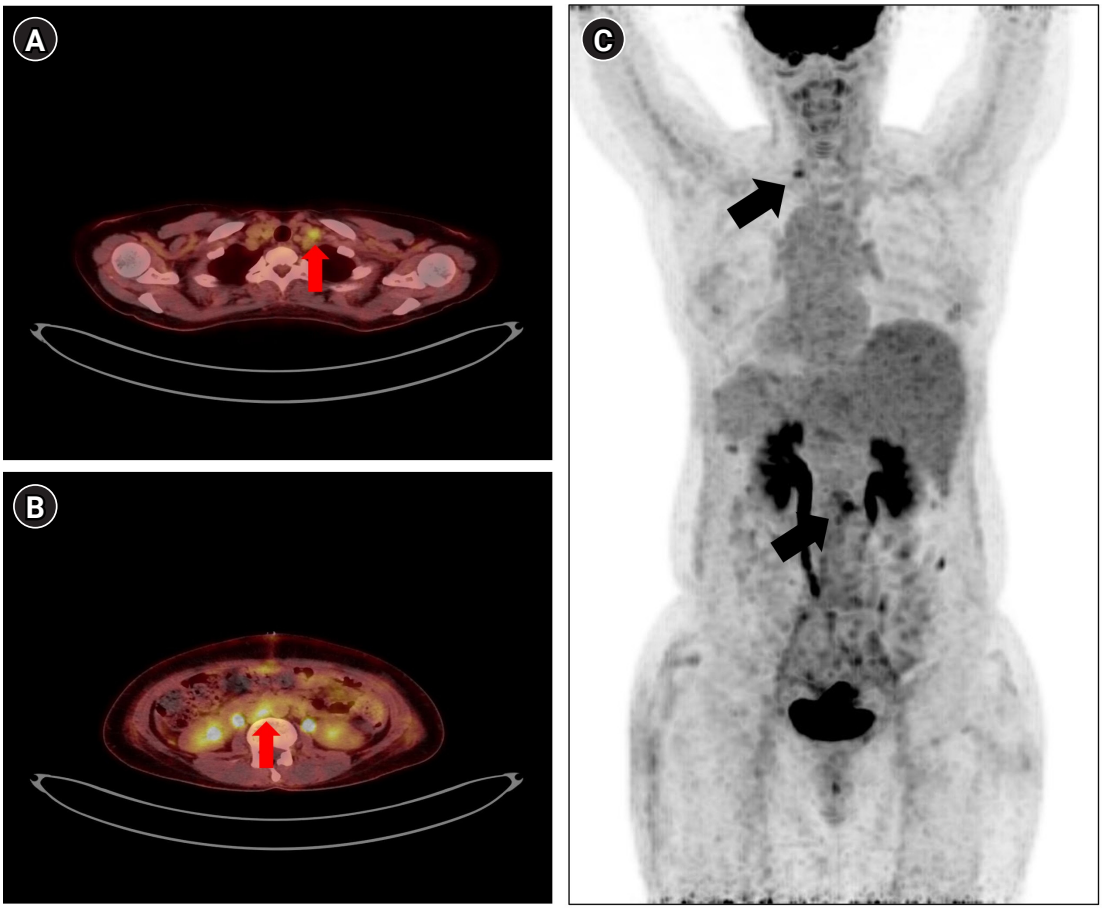

Fig. 1. Positron emission tomography (PET) image of patient number 1 in Table 1. Two isolated high standardized uptake values (SUVs), in the left supraclavicular lymph node (A, C: maximum SUV 5.6) and aortocaval area (B, C: maximum SUV 6.6) in the PET image (red and black arrows).

3. Results

Adjuvant radiation therapy was successfully completed in all patients. The median age was 49.25 years, ranging from 46 to 54 years. All patients had FIGO stage 4B disease. *BRCA* mutations were identified in two patients (*BRCA1* mutation and *BRCA2* mutation, respectively). All patients underwent adjuvant radiation therapy for a previous lymph node metastatic lesion during PARP inhibitor maintenance. There were no grade 3, 4, or worse acute adverse events related to radiation therapy. The only radiation-related adverse effect was erythematous pigmentation in one patient (patient 1 in Table 1). The median follow-up time was 36.75 months, ranging from 19 to 45 months. All patients achieved a complete response. None of the patients experienced disease recurrence or died during the follow-up period. Detailed clinicopathological characteristics of the four patients are shown in Table 1.

Discussion

The standard treatment of EOC currently involves a multimodal approach that includes PDS, chemotherapy, and tailored maintenance therapies [1]. The extent of lymph node dissection depends on various factors, including the extent of the tumor, the patient's overall health, and the surgical team's decision [4]. The primary goal is maximizing successful treatment chances while minimizing surgical risks.

An optimal debulking surgery remains the most significant prognostic factor in advanced EOC treatment. Leaving less than 1 cm of residual tumor after debulking surgery is associated with an increased survival advantage in contrast to leaving more than 1 cm of residual tumor

Table 1. Clinicopathological characteristics of each patient

Patient no.	Age (yr)	FIGO stage	Histology	Preoperative tumor marker (CA-125)	Primary debulking surgery	Adjuvant chemotherapy	*BRCA* mutation	Maintenance treatment	Metastatic lymph node lesion (PET-CT)	Radiation therapy (lesion)	Follow-up duration (mo)	Current status
1	49	4B	High-grade serous	627 IU/mL	TAH BSO omentectomy BPLND multiple metastasectomy LAR	Weekly paclitaxel-carboplatin (9 cycles)	*BRCA2* mutation	Olaparib	Lt. SCN Aortocaval area	Lt. neck, PAN	42	CR (NED)
2	48	4B	High-grade serous	848 IU/mL	TAH BSO omentectomy BPLND subdiaphragm peritoneum stippling multiple metastasectomy	Weekly paclitaxel-carboplatin (9 cycles)	*BRCA* wild type	Niraparib	Rt. SCN Both parasternal space Common hepatic area Para-aortic area	Rt. neck, PAN	45	CR (NED)
3	46	4B	High-grade serous	4,772 IU/mL	TAH BSO BPLND omentectomy multiple metastasectomy sigmoidectomy	Weekly paclitaxel-carboplatin (9 cycles)	*BRCA1* mutation	Niraparib	Lt. SCN Lt. second internal mammary space Aortocaval area Para-aortic area Both common iliac, external iliac, obturator areas	Lt. neck, PAN	41	CR (NED)
4	54	4B	High-grade serous	905 IU/mL	TAH BSO omentectomy BPLND multiple metastasectomy appendectomy	Weekly paclitaxel-carboplatin (9 cycles)	*BRCA* wild type	Niraparib	Lt. SCN Retrocaval area Aortocaval area Para-aortic area Rt. common iliac areas	Lt. neck, PAN	19	CR (NED)

FIGO, International Federation of Gynecology and Obstetrics; CA-125, cancer antigen-125; PET-CT, positron emission tomography-computed tomography; TAH, trans abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; BPLND, bilateral pelvic lymph node dissection; LAR, low anterior resection; Lt., left; Rt., right; SCN, supraclavicular lymph nodes; PAN, para-aortic lymph nodes; CR, complete remission; NED, no evidence of disease.

[7]. Suboptimal surgery has a negative effect on survival; thus, interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT) could be an alternative if complete cytoreduction is not possible [8,9]. IDS after NACT and PDS are two surgical approaches used in the management of advanced EOC. While both techniques aim to achieve optimal cytoreduction, they differ in the timing of surgery. IDS is often performed after a course of NACT, which helps to shrink the tumor and decrease tumor burden to decrease surgical complexity and postoperative complications. IDS following NACT is associated with a higher rate of optimal debulking surgery in advanced EOC than in PDS [10]. While NACT can effectively reduce the tumor size, there is a risk of disease progression during chemotherapy, leading to a decrease in the chance of optimal cytoreduction [11]. This risk highlights the importance of careful patient selection for IDS and vigilant monitoring of disease response during NACT. Based on these results, there are no accurate and broadly used indications for NACT. Moreover, if optimal debulking is anticipated, PDS should be performed with preference [12]. Cases in the present study showed distant lymph node metastasis to para-aortic and supraclavicular nodes. In addition, all four cases showed surgical results of minimal residual tumors (residual tumor of <1 cm) except for the distant para-aortic and supraclavicular lymph nodes. Maintaining treatment without complications that can cause discontinuation of standard frontline therapy for ovarian cancer is essential. The excision of extra-pelvic lymph node metastases in advanced ovarian cancer requires a prolonged surgical time and a substantially more complex procedure [13]. Moreover, lymphadenectomy with bulky nodes in advanced ovarian cancer is technically a different procedure than that in early ovarian cancer. Zang et al. [14] reviewed 25 patients with EOC who were initially diagnosed with extra-abdominal metastases. Their study demonstrated that patients with supraclavicular lymph node metastasis had a better prognosis than those with other stage 4 EOC. This clinical perspective indicates that lymphadenectomy in advanced ovarian cancer be performed subsequent to a prolonged and complicated surgical procedure, and it is correlated with high mortality and morbidity [3].

The optimal approach for managing oligometastatic progression in recurrent ovarian cancer is similarly debatable. There are a few published studies in which various therapeutic strategies were used to manage oligometastatic disease in recurrent ovarian cancer. A study by Palluzzi et al. [15] reviewed the data of 30 patients with ovarian cancer with oligometastatic progression while undergoing maintenance therapy with PARP inhibitors. Ten patients (33%) were treated with surgery, and 20 patients (67%) were treated with stereotactic radiotherapy. In this study, patients with peritoneal recurrences were primarily treated with surgery, while nodal recurrences were treated with stereotactic body irradiation. There were few severe side effects and no difference in survival benefit between the two approaches. Treatment for ovarian cancer is highly individualized. Surgeons are faced with the challenge of balancing performance of optimal cytoreduction and the potential hazards associated with complete removal of all metastatic lymph nodes. Adjuvant radiation therapy after PDS is a beneficial alternative to surgical excision for lesions with high surgical morbidity. Selective adjuvant radiation therapy allows targeted treatment by focusing on involved lymph nodes while sparing uninvolved areas. Based on molecular knowledge, ovarian cancer is radiation-sensitive, and technological advances in radiation treatment for ovarian cancer patients have regained appeal. By avoiding unnecessary surgical interventions, the risk of complications can be reduced [16]. Additionally, concurrent delivery of radiation therapy with maintenance therapy, such as PARP inhibitors, may enhance treatment efficacy by targeting both systemic and loco-regional disease control. However, the current evidence is limited, and patient selection criteria play a crucial role in identifying those most likely to benefit from this modality.

When a patient presents with metastatic lymph nodes, it is essential to identify the primary metastatic lesions before initiating standard treatment. In the present cases, subsequent chemotherapy was administered to all four patients who had undergone PDS, and the patients achieved CR before maintenance treatment with PARP inhibitor. From the molecular perspective of advanced EOC, even if imaging findings indicate CR, there is a high possibility that residual microscopic lesions remain, necessitating adjuvant treatment [17]. Extra-abdominal lymph node lesions were confirmed by fine needle aspiration biopsy, and intra-abdominal extra-pelvic lymph node lesions were confirmed by intraoperative biopsy. The application of PET-CT imaging at the initial evaluation allows precise identification of the origin of histologically proven meta-

static lymph nodes [18].

Our study had several limitations. First, it was a retrospective, single-center study; this study is subject to biases inherent to this research design, including potential selection and information bias. Second, the number of cases is small. With only four patients in this study, it may not represent the broader population of patients with stage 4B EOC. The absence of a control group of patients who did not undergo selective adjuvant radiation therapy restricts our ability to draw direct causative conclusions from our results. Increasing the size of the sample and expanding the patient cohorts would yield statistically valid outcomes. However, case reports or case series provide a platform for researchers to share their clinical experiences, highlight rare or distinctive manifestations, and convey instructive messages [19]. It underscores the point that even a limited number of cases can have meaningful clinical implications. Third, the median follow-up of less than 4 years might not be sufficient to determine long-term outcomes or potential late complications of radiation therapy. More data and further prospective studies are needed to investigate whether the efficacy and safety of selective adjuvant radiation therapy for distant lymph node metastatic lesions are suitable for the treatment of advanced ovarian cancer.

In conclusion, the management of distant lymph node metastasis in EOC remains controversial. Selective adjuvant radiation therapy in frontline treatment for ovarian cancer appears feasible, providing targeted treatment and sequential maintenance therapy with PARP inhibitors.

Article information

Conflicts of interest

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

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Author contributions

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Case report

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Drug-induced immune-mediated thrombocytopenia due to bevacizumab-FOLFOX therapy: a case report

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Drug-induced immune thrombocytopenia (DITP) is a very rare disease, with an estimated annual incidence of 10 cases per million. Oxaliplatin and irinotecan are widely used as chemotherapy for high-risk stage II and III colorectal cancer, and DITP has been reported to occur in patients using those agents. To treat unresectable metastatic colorectal cancer, bevacizumab is used in combination with oxaliplatin or irinotecan, and there have been a few reports of DITP cases in patients receiving that regimen. In this report, we describe a 68-year-old male patient with metastatic colon cancer (*KRAS* mutant type) to the liver and lung who developed acute immune-mediated thrombocytopenia due to bevacizumab-FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) therapy. During treatment, he showed purpura in his lower extremities on 21st cycle day 2. Lab work revealed a platelet count of less than 2,000/μL, reflecting a decrease from 135,000/μL at the start of the cycle 1 day prior. He did not have any other types of cytopenia or significant changes in laboratory findings. We diagnosed DITP due to bevacizumab-FOLFOX, and the patient did not show isolated thrombocytopenia after switching to Ziv-aflibercept-FOLFIRI (5-fluorouracil, leucovorin, and irinotecan).

Keywords: Bevacizumab; Chemotherapy; Colorectal neoplasms; Oxaliplatin; Thrombocytopenia

Introduction

Drug-induced thrombocytopenia occurs when certain medications destroy platelets or hinder the body's platelet production. Two distinct types of drug-induced thrombocytopenia exist: immune and nonimmune. Drug-induced nonimmune thrombocytopenia arises when a medication hampers the bone marrow's ability to produce an adequate quantity of platelets. On the other hand, drug-induced immune thrombocytopenia (DITP), a medication prompts the body to generate antibodies that target and destroy platelets. DITP is a very rare disease, with an estimated annual incidence of 10 cases per million people [1]. However, this number may be underestimated as DITP is not always recognized as a cause of thrombocytopenia and can be misdiagnosed or diagnosed with delay [2]. Although thrombocytopenia is a common side effect of chemotherapy caused by myelosuppression affecting all blood cell types, DITP is characterized by isolated thrombocytopenia instead of bicytopenia or pancytopenia. Anticancer drugs such as fludarabine, dactinomycin, cisplatin, oxaliplatin, and irinotecan have been reported as rare causes of DITP [3-5]. In the treatment of high-risk stage II and III colorectal cancer, oxaliplatin and irinotecan are commonly used in

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adjuvant chemotherapy regimens and have been reported to cause DITP [6-9]. However, for patients with unresectable metastatic colorectal cancer, targeted therapies are often combined with oxaliplatin or irinotecan, and reports of DITP in patients receiving such combination treatments are rare.

The authors report a rare case of DITP in a patient receiving bevacizumab-FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) therapy as palliative treatment for unresectable metastatic colorectal cancer. In this report, the authors aim to provide a literature review on DITP and highlight the importance of recognizing and managing this rare complication in cancer patients.

Case

Ethical statements: The study protocol was reviewed and approved by the Institutional Review Board of the Dong-A University College of Medicine (DAUHIRB-23-056). Informed consent for publication of clinical data was obtained from the case patient.

A 68-year-old male was admitted for palliative chemotherapy for metastatic colorectal cancer. He had undergone self-expandable metal stent insertion due to colorectal cancer-related obstruction (Fig. 1), followed by laparoscopic anterior resection and metastasectomy of the liver and lung. However, residual cancer was found in the resected liver metastasis, rendering further surgery impossible (Fig. 2). Therefore, the patient was treated with systemic

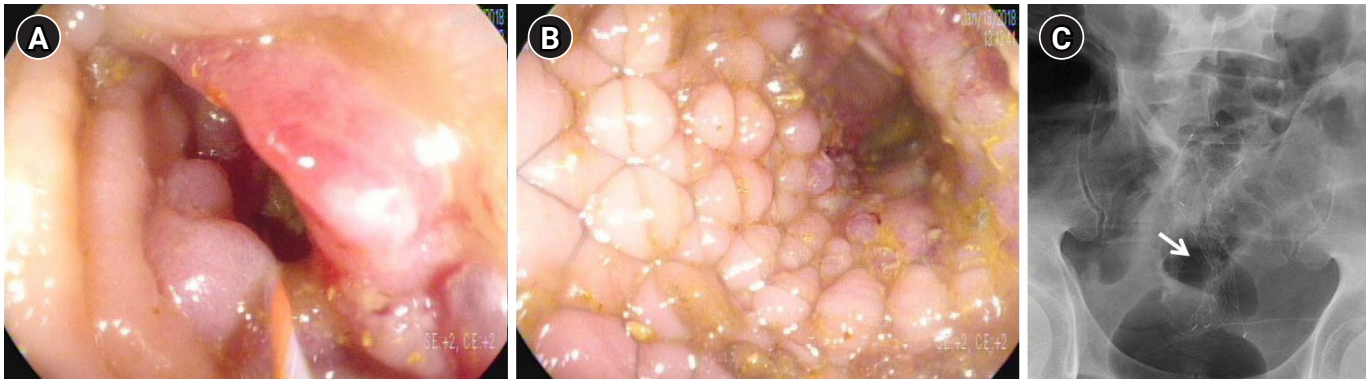

Fig. 1. Sigmoidoscopy showed an obstruction due to a mass in the sigmoid colon. (A) A self-expandable metal stent (SEMS) was inserted. (B) Fluoroscopy showed the successful placement of SEMS. (C) An abdominal X-ray confirmed the successful placement of the SEMS (arrow).

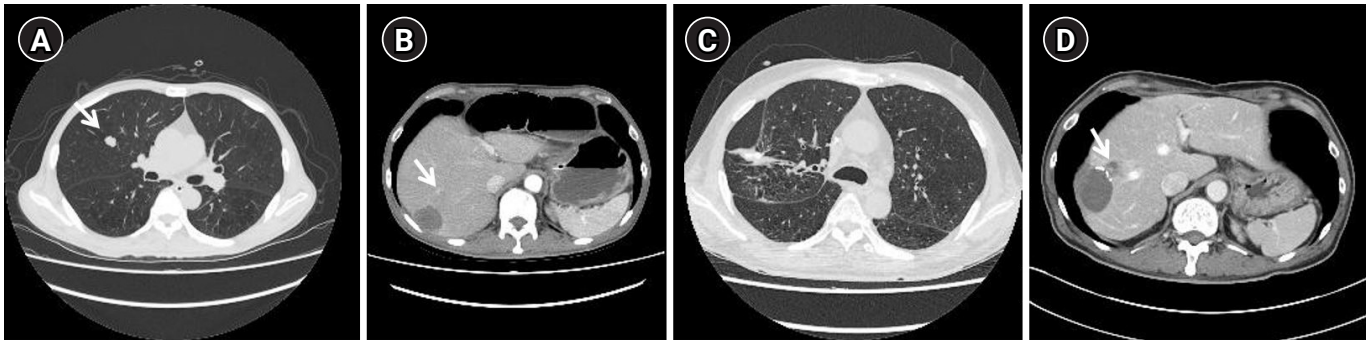

Fig. 2. Abdominal computed tomography. (A, B) Metastatic lesions (arrow) in the lung and liver. (C, D) Laparoscopic anterior resection and metastasectomy of the liver and lung were performed; however, residual cancer remained at the site of hepatic metastasectomy after the operation (arrow).

chemotherapy using FOLFOX in combination with bevacizumab, a vascular endothelial growth factor (VEGF) monoclonal antibody agent, as the patient was found to be epidermal growth factor receptor (EGFR)-positive but *KRAS*-mutant by immunohistochemistry. After 20 cycles of chemotherapy, the patient did not report any significant side effects, and based on RECIST criteria, was found to have stable disease on computed tomography (CT) scans conducted every three cycles.

Therefore, the patient started receiving the 21st cycle of bevacizumab-FOLFOX. During the physical examination, no specific findings were observed, and vital signs were stable with a blood pressure of 120/80 mmHg, a body temperature of 36.4 °C, a pulse rate of 89 beats/min, and a respiratory rate of 16 breaths/min. Laboratory findings showed white blood cells at 5,850/μL, hemoglobin at 14.2 g/dL, platelets at 135,000/μL, creatinine at 0.72 mg/dL, C-reactive protein at 0.09 mg/dL, prothrombin time at 12 seconds, and international normalized ratio at 1.08. Other findings were aspartate aminotransferase at 24 U/L, alanine aminotransferase at 5 U/L, albumin at 4.1 g/dL, total bilirubin at 0.5 mg/dL, serum sodium at 135 mmol/L, and serum potassium at 4.7 mmol/L, all within normal limits. The polymerase chain reaction for coronavirus disease 2019 was negative. Chemotherapy was started on the 2nd day of hospitalization, with bevacizumab at a dose of 5 mg/kg intravenously for a total of 270 mg, and oxaliplatin at a dose of 85 mg/m^2 for a total of 130 mg, without any specific changes. On the 3rd day of hospitalization, which was the 2nd day of chemotherapy, purpura was observed in both lower extremities (Fig. 3A, 3B). In the blood test, platelets were measured to be less than 2,000/μL, and the same value was confirmed on retesting, indicating a rapid decrease in platelets. Depending on the Common Terminology Criteria for Adverse Events, it can be classified as grade 4, an adverse event that seriously interferes with life. Although hemoglobin decreased to 11.5 g/dL, there were no other bleeding signs except for purpura on the limbs. There were no significant changes in other blood cell disorders, prothrombin, aminotransferase, bilirubin, creatinine, lactate dehydrogenase, or electrolytes. Additionally, no abnormalities were observed in peripheral blood smears, including fragmented red blood cells, left shift, immature cells, or platelet aggregation, and coagulation tests, including D-dimer, were normal. Anti-platelet antibodies and platelet-associated antibodies were negative. Chemotherapy was immediately discontinued, and 320 mL of platelets in eight units were transfused. After the transfusion, the platelet count rose to 81,000/μL, and without additional transfusion, the patient was discharged after further observation with the platelet count maintaining at 67,000/μL on the 6th day of hospitalization and showed improvement in purpura on the limbs with no other bleeding signs (Fig. 3C). One week later, the platelet count was confirmed to be 212,000/μL in an outpatient visit (Fig. 4). Since the patient's platelets had recovered, no cytopenia was observed except for platelets, and no abnormalities

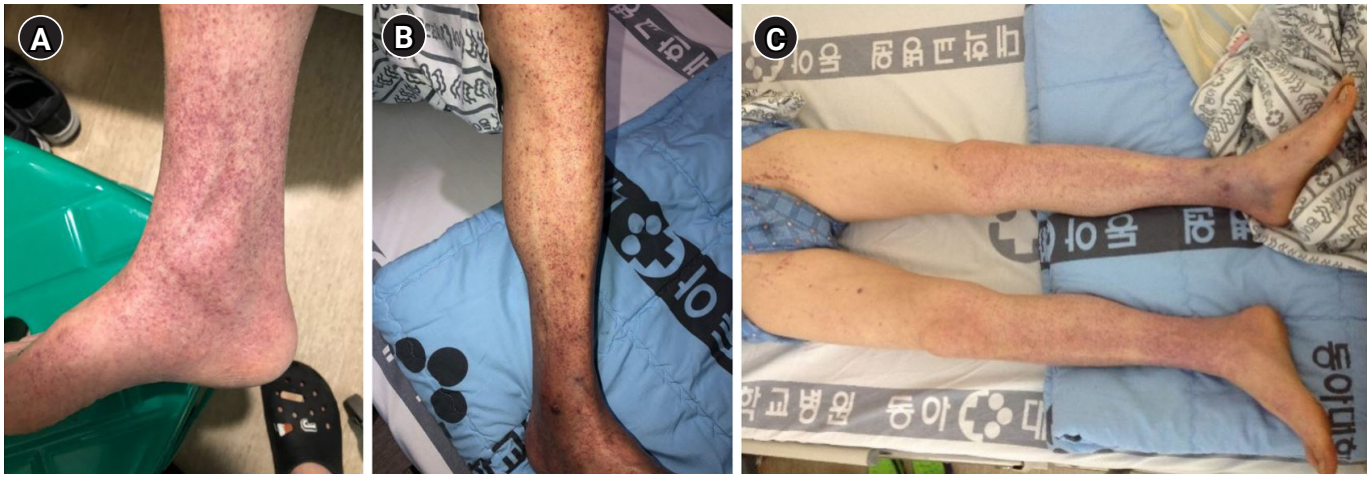

Fig. 3. The appearance of purpura on the patient's extremities. (A, B) On day 3 (cycle day 2), purpura was observed in the lower extremities. (C) On day 6, the purpura in the lower extremities was relieved.

were detected in the peripheral blood smear. Therefore, it was decided, in consultation with the hematologist, not to proceed with additional invasive tests such as a bone marrow biopsy for the patient.

After the last chemotherapy, a CT scan was performed, and the patient was confirmed to have progressive disease according to the response evaluation criteria in solid tumors (Fig. 5). After changing to Ziv-aflibercept-FOLFIRI (5-fluorouracil, leucovorin, and irinotecan), the patient underwent nine cycles of chemotherapy without a decrease in platelet count.

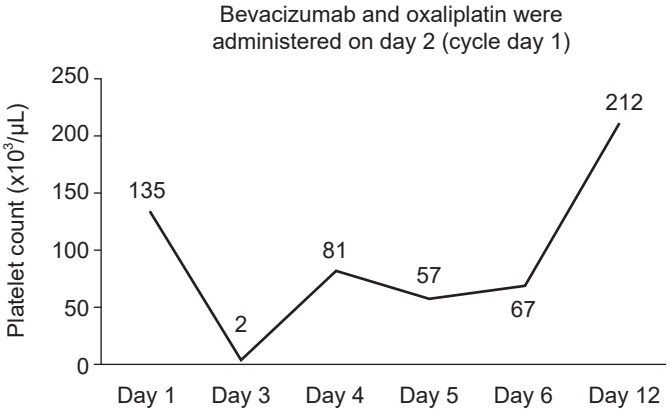

Fig. 4. Lab work demonstrated a platelet count of less than $2x10^3/\mu L$, reflecting a decrease from $135x10^3/\mu L$ at the start of the cycle 1 day prior. On day 12 (outpatient department), the platelet count returned to the normal range.

Discussion

For the treatment of unresectable metastatic colorectal cancer, combination chemotherapy based on FOLFOX containing oxaliplatin or FOLFIRI containing irinotecan is established as first-line treatment, with the addition of bevacizumab, a monoclonal antibody targeted therapy for VEGF, or cetuximab, a monoclonal antibody targeted therapy for EGFR [10]. FOLFOX is widely used for the treatment of high-risk stage 2 and stage 3 colorectal cancer [3]. Compared to cetuximab, which is effective only for left-sided colon cancer with positive EGFR and wild-type *KRAS* and *NRAS*, bevacizumab is relatively more applicable in the palliative treatment of metastatic colorectal cancer [11].

Oxaliplatin is commonly associated with peripheral neuropathy and asymptomatic pancytopenia, but there have also been reports of hypersensitivity reactions and isolated

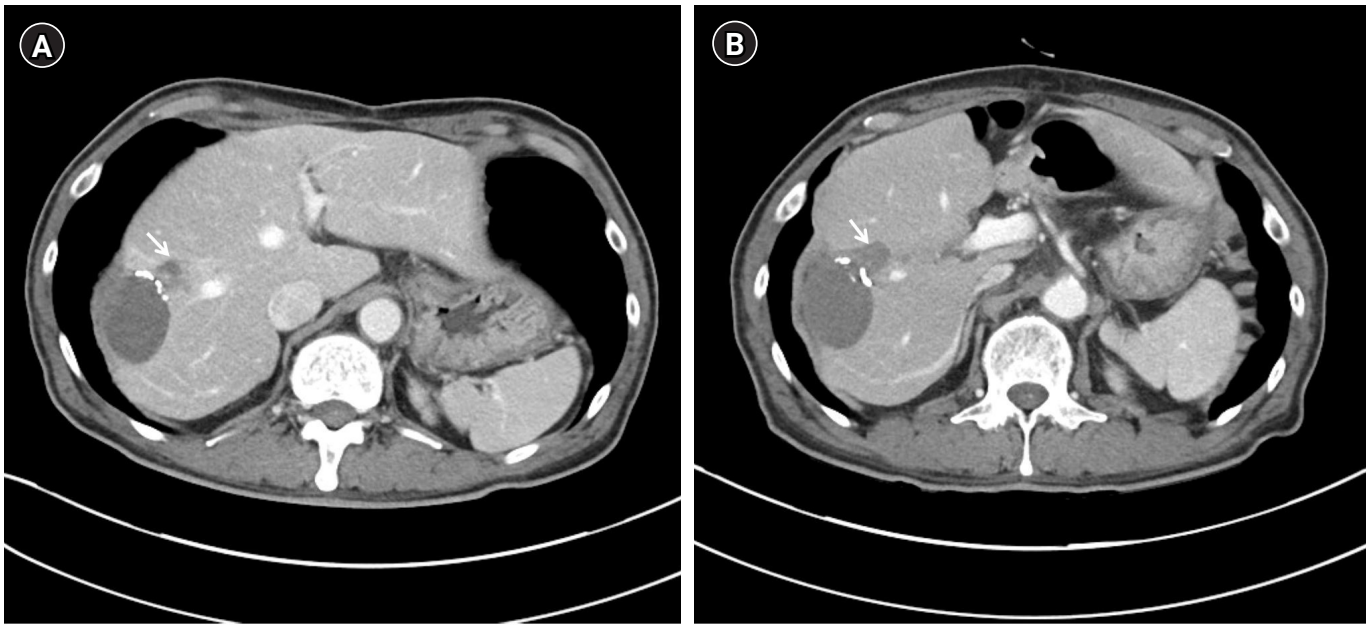

Fig. 5. Confirmation of progressive disease was achieved through comparison with the previous abdominal computed tomography. (A) After the 18th cycle of chemotherapy, an abdominal computed tomography scan revealed a soft tissue mass-like lesion (arrow) adjacent to the S8 wedge. (B) After the 21st cycle of chemotherapy, another abdominal computed tomography scan showed an increased extent of the soft tissue mass-like lesion (arrow), extending from the S8 wedge resection site to the hilum.

cases of thrombocytopenia [3,12]. There are three mechanisms for thrombocytopenia caused by oxaliplatin. The first mechanism is bone marrow suppression. A significant proportion of thrombocytopenia can be explained by bone marrow suppression. A study showed that thrombocytopenia was observed in 19% of patients treated with 5-fluorouracil/leucovorin alone, but in 77% of patients treated with oxaliplatin in combination, most of which could be explained by bone marrow suppression accompanied by anemia and leukopenia [3]. Although the mechanism is not clearly understood, it is believed that oxaliplatin induces apoptosis in megakaryocytes more than other drugs, leading to thrombocytopenia. This is accompanied by other blood cell decreases, occurs around 10 days after administration, is dose-dependent, and gradually appears, making it predictable. This is a major mechanism for causing thrombocytopenia [6]. The second mechanism is splenic sequestration caused by sinusoidal injury. Oxaliplatin is believed to cause thrombocytopenia through sinusoidal injury, which leads to secondary portal hypertension, splenomegaly, and sequestration of platelets [13,14]. According to a study conducted by M.D. Anderson in the United States, splenomegaly caused by oxaliplatin-based therapy can be measured using the splenic index. When comparing patients who received FOLFOX and those who received 5-fluorouracil/leucovorin, an increase in splenic index was observed in 45.7% and 16.3% of patients, respectively. Of those who developed splenomegaly, 28% experienced thrombocytopenia, while only 5% of patients without splenomegaly had this complication [15]. The third mechanism is immune-mediated thrombocytopenia. Although the exact mechanism of platelet destruction is not fully understood, it can be associated with weakly binding antibodies to platelet membrane antigens. Drug-dependent anti-platelet antibodies to specific drugs such as oxaliplatin can also cause platelet destruction and thrombocytopenia through interaction with antigens. This immune-mediated thrombocytopenia caused by these drugs usually occurs within 2 weeks of exposure, with some cases appearing rapidly within a few hours. Platelet counts often drop to less than 20,000/μL and are unpredictable [16]. However, considering a rare case report in which myelodysplastic syndrome was diagnosed through a bone marrow biopsy in a gastric cancer patient experiencing gradual thrombocytopenia using FOLFOX, it would be necessary to consult with a hematologist for evaluation if hematologic malignancies as the underlying cause of thrombocytopenia cannot be ruled out [17].

In this case, the patient exhibited isolated thrombocytopenia without reductions in other blood cells. The rapid onset of a sudden decrease, rather than a gradual decline, suggests the possibility of immune-mediated thrombocytopenia rather than bone marrow suppression. Abdominal CT did not reveal splenomegaly, and there were no significant decreases in other blood cells apart from platelets. Additionally, no abnormal findings were observed in the peripheral blood smear, supporting the clinical plausibility of a diagnosis of DITP. The authors attempted to confirm the presence of drug- dependent anti-platelet antibodies using flow cytometry, but due to limitations in hospital resources, this was not feasible. While the presence of drug-dependent anti-platelet antibodies may support the diagnosis, it is not a prerequisite. Clinical diagnosis of DITP can be made by observing whether platelet count recovers after discontinuing the drug. A negative result for drug-dependent anti-platelet antibodies does not exclude the diagnosis [18]. Also, it can be difficult for most medical institutions to confirm drug-dependent anti-platelet antibodies for a specific drug, and the process of obtaining test results can take several days or longer. Therefore, immediate diagnosis and drug discontinuation should be determined through clinical diagnosis. However, it may be difficult to determine which drug is causing DITP through clinical diagnosis alone. Bevacizumab, administered along with FOLFOX, can cause fatal side effects such as hypertension, proteinuria, thrombosis, and gastrointestinal perforation [19]. Compared to reports of oxaliplatin, a component of FOLFOX, being a causative agent of immune-mediated thrombocytopenia in some studies, reports of immune-mediated thrombocytopenia caused by bevacizumab are rare [7-9,20]. In this case, after the last administration of bevacizumab-FOLFOX, the patient was found to have progressive disease on follow-up abdominal CT and had to switch to another chemotherapy regimen, Ziv-aflibercept FOLFIRI, after which there was no recurrence of thrombocytopenia. Therefore, the cause of thrombocytopenia, in this case, was diagnosed as DITP caused by bevacizumab-FOLFOX. Based on previous studies, oxaliplatin is the most commonly reported drug among the administered drugs, making it the most likely cause, but the

possibility of bevacizumab cannot be ruled out. Although the exact cause of the DITP was not determined by identifying drug-dependent platelet antibodies, it is important to make a clinical judgment in the diagnosis of DITP. The fact that no recurrence was observed after changing the anticancer therapy and understanding the mechanism of DITP is significant.

The authors report a rare case of DITP that occurred during palliative chemotherapy for unresectable metastatic colon cancer, along with a literature review.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: JYL. Data curation: JYL. Formal analysis: JYL. Investigation: MK, JHL, JYL. Methodology: MK, JHL, JYL. Project administration: MK, JHL, JYL. Supervision: JHL, JYL. Validation: MK, JHL, JYL. Visualization: MK, JHL, JYL. Writing - original draft: MK, JYL. Writing - review & editing: MK, JHL, JYL.

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Corrigendum

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Corrigendum to: Unusual Magnetic Resonance Imaging Findings Contrast-induced Encephalopathy following Cerebral Angiography

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IV. ETHICAL CONSIDERATIONS

Authorship

The KMJ accepts authorship criteria recommended by the ICMJE (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) and the Good Publication Practice Guidelines by the Korean Association of Medical Journal Editors (KAMJE, 2019, http://kamje.or.kr).

Each author is expected to have made a substantial contribution to the conception or design of the work; the acquisition, analysis, or interpretation of data; the creation of new software used in the work; or have drafted the work or substantively revised it; AND to have approved the submitted version (and any substantially modified version that involves the author's contributions to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even those in which the author was not personally involved, are appropriately investigated and resolved, and the resolution documented in the literature.

Those who do not meet the above criteria should be acknowledged as contributors rather than authors. The corresponding author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.

Contributor Roles Taxonomy (CRediT)
- Conceptualization
- Data curation
- Formal analysis
- Funding acquisition
- Investigation
- Methodology
- Project administration
- Resources
- Software
- Supervision
- Validation
- Visualization
- Writing – original draft
- Writing – review and editing

The KMJ accepts notice of equal contributions for the first or corresponding authors when the study was clearly performed by co-first or co-corresponding authors. The KMJ does not allow authorship corrections after publication unless the editorial staff made an obvious mistake. Before publication, authorship can be changed if all authors request the authorship correction.

Declaration of ethics including authorship

The corresponding author must agree to abide by research ethics guidelines, including those involving authorship, by including the following sentences in a cover letter.

"All of the bylined authors meet the ICMJE criteria for authorship. We well understand the privilege and responsibility of authorship of scientific publications. We declare that we are following global and/or local guidelines of research and publication ethics strictly including authorship."

All authors should provide details of their position in the affiliated institution on the online submission system (e.g., professor, college lecturer, graduate student, researcher, college student, post-doctoral fellow, middle or high school teacher, or high school student, etc.).

Redundant publication and plagiarism

Redundant publication is defined as "reporting (publishing

or attempting to publish) substantially the same work more than once, without attribution of the original source(s)." Characteristics of reports that are substantially similar include the following: (a) "at least one of the authors must be common to all reports (if there are no common authors, it is more likely plagiarism than redundant publication)," (b) "the subjects or study populations are the same or overlapped," (c) "the methodology is typically identical or nearly so," and (d) "the results and their interpretation generally vary little, if at all."

When submitting a manuscript, authors should include a letter informing the editor of any potential overlap with other already published material or material being evaluated for publication and should also state how the manuscript submitted to the KMJ differs substantially from other materials. If all or part of a patient population was previously reported, this should be mentioned in the Methods, with citation of the appropriate reference(s). The duplication will be checked through crosscheck (https://app.ithenticate.com) or eTBLAST (https://bio.tools/etblast) before submission. If duplicate publication related to the papers in this journal is detected, the manuscripts may be rejected, the authors will be announced in the journal, and their institutes will be informed. There will also be penalties for the authors.

Secondary publication

It is possible to republish manuscripts if the manuscripts satisfy the conditions for secondary publication in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals established by the ICMJE (http://www.icmje.org).

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

Conflict of interest statement

The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data. Examples of potential conflicts of interest are financial support from or connections to pharmaceutical companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.

Commercial sponsorships or funding

The corresponding author must inform the editor of any commercial sponsorships or fundings.

Registration of the clinical trial research

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

Data-sharing statement

The KMJ accepts the "ICMJE Recommendations for Data Sharing Statement Policy." All manuscripts reporting clinical trial results from July 1, 2018 should submit a data-sharing statement following the ICMJE guidelines. Authors can refer to the editorial, "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee

of Medical Journal Editors," in JKMS Vol. 32, No. 7:1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

Statement of informed consent and IRB approval

Copies of written informed consent and institutional review board (IRB) approval for clinical research (original article and case report) should be kept. Authors should include the IRB approval number in the manuscript. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct. For studies involving human subjects, the method through which informed consent was obtained from the participants must be stated in the Methods section.

Statement on human and animal rights

Clinical research should be done in accordance with the Ethical Principles for Medical Research Involving Human Subjects, as outlined in the Helsinki Declaration (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. For publication, the human subjects' identifiable information, such as the patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, the research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

Process to manage the research and publication misconduct

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

Errata

Errata provide a means of correcting errors that occur during the writing, typing, editing, or publication (e.g., a misspelling, dropped word or line, or mislabeling of a figure) of a published article. Errata can be submitted through the KMJ online manuscript management portal as a Microsoft Word file. In the Abstract section of the submission form (a required field), enter "Not Applicable" and upload the text of the proposed erratum. Please see a recent issue for correct formatting.

Author corrections

If the addition or deletion of authors or a change to the order of authorship is required, the corresponding author must complete the authorship change form and submit it through the KMJ online manuscript management portal with the signature of all existing authors and new authors. In the Abstract section of the submission form (a required field), enter "Not Applicable." The text of the proposed erratum should be uploaded as a Microsoft Word file. When there is a request for a change by the author, the editorial committee assembles an ethics committee to judge whether the change is appropriate. If a new author should be added or an author should be deleted after submission, it is the responsibility of the corresponding author to ensure that all authors are aware of and agree to the change in authorship. The KMJ assumes no responsibility for such changes. Please see a recent issue for correct formatting.

Retractions

Retractions are reserved for major errors or breaches of ethics that, for example, may call into question the source of the data or the validity of the results and conclusions of an article. Retractions should be submitted through the KMJ online manuscript management portal as a Microsoft Word file. In the Abstract section of the submission form (a required field), put "Not Applicable." Letters of agreement signed by all of the authors must be supplied as Miscellaneous Files Not for Publication (scanned PDF files). The retraction will be assigned to the journal's editor-in-chief, and the editor who handled the paper and the chair of the KMJ editorial board will be consulted. If all parties agree to the publication and content of the retraction, it will be sent

to the journals department for publication.

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

V. MANUSCRIPT PREPARATION AND FORMAT

1. General requirements

- Every manuscript should be written in English.
- The main document, including manuscript text and tables, should be prepared in MS Word.
- The manuscript should be double-spaced on 21.6 × 27.9 cm (US letter) or 21.0 × 29.7 cm (A4) paper with top, bottom, right, and left margins of 3.0 cm.
- All manuscript pages are to be numbered consecutively, beginning with the abstract as page 1. Neither the authors' names nor their affiliations should appear on the manuscript pages.
- Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. A spelled-out term followed by the abbreviation in parentheses should be used on first mention unless the abbreviation is widely recognized (e.g., UN for United Nations).
- The names of manufacturers of equipment and non-generic drugs should be given.
- When quoting from other sources, supply a reference number after the author's name or at the end of the quotation (see References section).
- Authors should express all measurements in conventional units, using the International System (SI) of units.
- To make papers more readable and informative, mark the followings in italics.
  - Biological names of organisms: *Saccharomyces cerevisiae*, *E. coli*
  - Restriction enzymes and some enzymes: *EcoRI, Taq polymerase*
  - Names of genes: *src, c-H-ras, myc*
  - Latin words: *in vivo, in vitro, in situ*
  - Centrifugal acceleration: *g* (e.g., 100,000 *g*)

2. Reporting guidelines for specific study designs

Research reports frequently omit important information. As such, reporting guidelines have been developed for a number of study designs, and some journals may ask authors to follow them. Authors are also encouraged to consult the reporting guidelines relevant to their specific research design. A good source for reporting guidelines is the EQUATOR Network (http://www.equator-network.org/home) and the United States National Library of Medicine (http://www.nlm.nih.gov/services/research_report_guide.html).

3. Original articles

Manuscript style

The manuscript should be prepared according to the "ICMJE Recommendations for the Conducts, Reporting, and Publication of Scholarly Work in Medical Journals" (2021) (http://www.icmje.org). In addition to the ICMJE recommendation, a number of reporting guidelines have been developed by experts to facilitate reporting of research studies or clinical trials (http://www.equator-network.org/library). For reporting of randomized controlled trials, the KMJ requires compliance with the CONSORT statement (http://www.consort-statement.org) and the ICMJE Statement on Data Sharing (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html).

Manuscript components

The manuscript, including tables and their footnotes and figure legends, should use the 12-point Times New Roman font and line spacing should be set to "double." The manuscript should be in the following sequence: title page, Conflicts of interest, Sources of funding, Author contributions, ORCID iDs, Abstract and Keywords, Introduction, Methods, Results, Discussion, Acknowledgments, References, Tables (each table complete with a title and footnotes), and Figure Legends (figures should be uploaded separately, not embedded in text). All pages should be numbered consecutively starting from the title page. All numbers should be written in Arabic numerals throughout the manuscript except for the first word of a sentence. Tables and figures should not be inserted in the main text. A combined table file can be uploaded separately from the main manuscript file. A combined figure file or individual figure files can be uploaded separately from the main manuscript.

File formats

Drawings, photographs, graphs, or combined figures can be submitted as PDF files. We accept graphic files in the PDF, JPEG, or TIFF formats only. It is permissible to send low-resolution images for peer review, but we will ask for high-resolution files before publication. Acceptable file formats for supplemental video files are mov, wmv, mpg, mpeg, and mp4. The file size and running time of each video should be no more than 25 MB and 5 minutes, respectively.

Title page

Include the following items on the title page: (1) the title of the manuscript (the title should be short, informative, contain the major keywords, and be no more than 200 characters in length, including spaces between words; acronyms and abbreviations should be avoided, and the species of any experimental animal must be indicated in the title; (2) an author list (include ORCID*); (3) the names of each author's institutional affiliation; (4) the name, address, telephone number, and email address of the corresponding author; (5) the source of any research funding, if any, and a list of where and when the study has been presented in part elsewhere; and (6) a running title of no more than 50 characters.

*ORCID: We recommend that the open researcher and contributor ID (ORCID) of all authors be provided. Authors can obtain an ORCID at http://orcid.org. Registration is free to every researcher in the world.

Conflict of interest

State any potential conflict of interest that could influence the authors' interpretation of the data, such as financial support from or connections to pharmaceutical companies, political pressure from interest groups, or academically related issues.

Author contributions

What authors have contributed to the study should be described in this section. To qualify for authorship, all contributors must meet at least one of the 12 core contributions defined by CRediT (conceptualization, methodology, software, validation, formal analysis, investigation, data curation, funding acquisition, project administration, resources, supervision, and visualization), as well as at least one writing contribution (original draft preparation, review, and editing). Authors may also satisfy the other remaining contributions; however, these alone will not qualify them for authorship.

Contributions will be published with the article, and they should accurately reflect contributions to the work. The submitting author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time.

An example:

Conceptualization: GDH. Data curation: YSJ, YC. Formal analysis: CSK. Methodology: YK, GDK.; Software: YK, YSJ. Validation:..... Investigation:..... Funding acquisition:..... Project administration:..... Resources:..... Supervision:..... Visualization:..... Writing - original draft: GDH, YSJ. Writing - review and editing: YC, YK, CSK.

Abstract and keywords

The abstract should briefly describe the content of the manuscript in a structured format within 250 words. The abstract should be structured as follows; Background, Methods, Results, and Conclusion. Initialisms, acronyms and informal abbreviations should be avoided where possible; if needed, they should be kept to an absolute minimum and accompanied by proper definitions. Three to five keywords should be listed below the Abstract on the Abstract page. For the selection of keywords, refer to Medical Subject Headings (MeSH) in PubMed, or http://www.nlm.nih.gov/mesh/MBrowser.html.

Main text

- Introduction

A brief background, references to the most pertinent papers general enough to inform readers, and the relevant findings of others should be included. It is recommended that the introduction include a "General and specific background," "Debating issue," and "Specific purpose of this study."

- Methods

The explanation of the experimental methods used should be concise and sufficient for repetition by other qualified investigators. Procedures that have been published previously should not be described in detail. However, new or significant modifications of previously published procedures require full descriptions. Clinical studies or

experiments using laboratory animals or pathogens should mention approval of the studies by relevant committees in this section. The sources of special chemicals or preparations should be supplied, along with their location (name of company, city and state, and country). The method of statistical analyses and the criteria for determining significance levels should be described. An ethics statement should be placed in this section when the studies are performed using clinical samples or data, and animals. Examples are provided below.

(For clinical study)

The present study protocol was reviewed and approved by the Institutional Review Board of xxx XXXXXX of the University College of Medicine (approval No. 2018001). Informed consent was submitted by all subjects when they were enrolled.

(For animal study)

The procedures used and the care of animals were approved by the Institutional Animal Care and Use Committee at xxxXXXXX University (approval No. 2018002).

(For clinical trials)

This was a randomized clinical trial at the second phase, registered at the Clinical Research Information Service (CRIS, http://cris.nih.go.kr), number KCT0002018.

Other international registration is acceptable. Manuscripts reporting interventional clinical trial should include a data-sharing plan following the ICMJE statement by referring to the ICMJE Statement on Data Sharing.

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

• Results

This section should be presented logically and in a manner consistent with the Methods section. Tables and figures are recommended when they can present data more succinctly and clearly. Do not duplicate the content of tables or figures in the Results section. Briefly describe the core results related to the conclusion in the text when data are provided in tables or in figures. In the Results section, audio or video files are also welcomed. Supplementary results can be placed in an Appendix.

• Discussion

The data should be interpreted concisely without repeating materials already presented in the Results section. A summary or conclusion should be included at the end of this section. We recommend authors describe the clinical or biomedical significance of the study. Speculation is permitted but must be clearly supported by the results or literature published.

Acknowledgments

The authors can list the names of persons who helped plan or conduct the study but are not eligible authors in this section. Funding sources, which are supplied on the title page, should not be duplicated in this section.

References

References should be numbered in the order they appear in the text and should not exceed 40 in number. Citation of references in the text should be identified with Arabic numerals in square brackets (for example, ... the leading cause of death in Korea [1,2] and preceding any punctuation). References should be listed in the order they are cited in the text, with consecutive numbers in this section. The style for citing papers in periodicals is: last name and initials of all authors, full title of article, journal name abbreviated in accordance with the PubMed style, year, volume, issue number and first and last page numbers. The style for a chapter of a book is: author and title of the chapter, editor of the book, title of the book, edition, volume, publisher, year, and first and last page numbers. Up to six authors can be listed in a reference; the names of all authors after the first 6 should be abbreviated to "et al." The use of software to manage references (e.g., EndNote) is recommended.

Authors are responsible for the accuracy and completeness of their references and correct text citations. Papers in press may be listed among the references with the journal name and tentative year of publication. Gray literature

sources are not allowed for references. Internet materials are acceptable with the correct URL and the date accessed.
Examples of reference style:

1. Journal
   Kim TS, Kang SH, Kang PM, Ha H, Kim SD, Yoon J, et al. Clinical significance of serum neutrophil gelatinase-associated lipocalin in the early diagnosis of renal function deterioration after radical nephrectomy. Kosin Med J 2018;33:20-8.
   Verbalis JG. Renal physiology of nocturia. Neurourol Urodyn 2014;33(Suppl 1):S6-9.
2. Book
   Hong GD, Kim C, Park J. KMJ reference style: a guide for authors. 5th ed. Daehakro Press; 2017.
3. Chapter in a book
   Floch MH. Probiotics, probiotics and dietary fiber. In: Buchman A, editor. Clinical nutrition: a guide for gastroenterologists. SLAK Incorporated; 2005. p. 18-24.
4. Conference
   Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsale, Ireland. Springer; 2002. p. 182-91.
5. Internet or electronic resource
   Testa J. The Thomson Reuters journal selection process [Internet]. Thomson Reuters; c2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process

Tables and figures

Tables: Tables are to be numbered in the order in which they are cited in the text. A table title should concisely describe the content of the table so that a reader can understand the table without referring to the text. Each table must be simple and provided on a separate page with its title. Explanatory matter is placed in the footnotes below the table and not in the title. All non-standard abbreviations should be explained in the footnotes. The symbols a), b), c), d), should be used (in that order) for footnotes. Statistical measures such as standard deviation (SD) or standard error (SE) should be identified. No vertical or horizontal rules should appear between table cells.

Figures and legends for illustrations: Figures must be submitted as separate files in JPEG, TIFF or PDF format (do not embed the figures in a Microsoft Word file). To supply figures in other file formats, contact the editorial office. All images should the following image resolutions or greater: line art (an image composed of lines and text): 1,000 dpi; halftone (a continuous tone photograph, which contains no text): 300 dpi; or combination (line art and halftone): 600 dpi.

Photographs of recognizable persons should be accompanied by a signed release from the person in the photograph or an appropriate legal guardian authorizing reproduction. Written permission should be obtained for the use of all previously published illustrations (and copies of permission letters should be included).

Figures should be numbered, using Arabic numerals, in the order in which they are cited. In the case of multiple prints bearing the same number, use English letters immediately after the numerals to indicate the correct order. (e.g., Fig. 1A, Fig. 1B and C; Fig. 2A–D).

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Description of *p* value: p is always italicized and in lower case. When p values are statistically significant, the corresponding data should be marked with superscripted asterisks ($p<0.05$, $p<0.01$, $p<0.001$).

Abbreviations: Except for units of measurement, abbreviations are strongly discouraged. Do not use abbreviations in the title or abstract and limit their use in the text. Define all abbreviations at first mention.

Units of measurement: Laboratory values are expressed using conventional units of measure, with relevant System International (SI) conversion factors, if necessary expressed secondarily (in parentheses) only at first mention. Figures and tables should use conventional units, with conversion factors given in legends or footnotes. The metric system is

preferred for the expression of length, area, mass, and volume.

Names of drugs, devices, and other products: Generic names of pharmaceuticals should be used. When proprietary brands are used, include the brand name and the name of the manufacturer in parentheses after the first mention of the generic name in the Methods section.

Gene names, symbols and accession number: Authors describing genes or related structures in a manuscript should include the names and official symbols provided by the US National Center for Biotechnology Information (NCBI) or the HUGO Gene Nomenclature Committee.

Supplementary materials

Authors can submit supplementary materials for online-only publication when there is insufficient space to include the materials in the main article. Supplementary materials should be original and important to the understanding and interpretation of the report. As supplementary materials will not be edited or formatted after publication, authors are responsible for the accuracy and presentation of this material.

Supplementary materials should be submitted in a single MS Word document or a single PDF file, which should include all materials (information, tables, figures, and references). Each element included in supplementary material should be cited in the text of the main manuscript (e.g., Supplementary Table 1, Supplementary Fig. 1, Supplementary Methods). The first page of the online-only document should list the number and title of each element included in the document.

4. Review articles

Reviews are comprehensive analyses of specific topics. They are typically solicited by the Editor, but we also consider unsolicited material. Please send us a Presubmission Inquiry before writing a review article. All review articles undergo the same review process as other types of articles prior to acceptance. Reviews are organized as follows: title page, abstract (a single unstructured paragraph of no more than 250 words) and three to five keywords (as in MeSH), introduction, main text, conclusion, acknowledgments, references, tables, and figure legends. Reviews have no restrictions on word count or the number of figures and tables. However, authors should eliminate redundancies, emphasize the central message, and provide only the data necessary to convey that message. A review article is limited to less than 6,000 words, with a maximum of 100 references, excluding tables or figure legends.

5. Case reports

Case reports will be published only in exceptional circumstances, if they illustrate a rare occurrence of clinical importance. The manuscript should be in the following sequence: title page, abstract (no more than 250 words) and three to five keywords (as in MeSH), introduction, case(s), discussion, acknowledgments, references (no more than 20), tables, and figure legends. The manuscript should have no more than six tables or figures in total. For case reports involving humans, whether informed consent for publication of clinical data was obtained from the study participants must be stated in the case description section.

6. Editorials

Editorials are invited by the Editor and should provide commentary on articles in the current issue. Editorial topics could include active areas of research, fresh insights, and debates in all fields of interest to KMJ readers. Editorials should not exceed 1,000 words, excluding references, tables, and figure legends. No more than 20 references should be cited. The manuscript should have no more than three tables or figures. Any article longer than these limits should be discussed with the editor.

Table 1. Specifications for publication types

Type of article	Original article	Review article	Case report	Editorial
Abstract (words)	250	250	250	NR
Text (words)[a]	NL	6,000	1,500	1,000
References	40[b]	100	20	20
Tables and Figures	NL	NL	6	3

NL, not limited; NR, not required.
[a]Maximum number of words is exclusive of the abstract, references, and figure legends.
[b]Except meta-analyses or systematic reviews.

VI. INSTRUCTIONS FOR SUBMISSION OF REVISED MANUSCRIPTS

To prepare a revised version of your manuscript, authors should carefully follow the instructions given in the Editor's

letter. Failure to do so will delay a decision on a revision. If references, tables, or figures are moved, added, or deleted during the revision process, all subsequent tables, references, and figures should be renumbered to ensure they are cited in order.

Revised manuscript submissions should include a point-by-point response to the reviewers' comments. Authors should describe how each comment was addressed or why it was not be addressed, and clearly indicate which paragraph was revised to address each comment. The response to reviewers will be shared with all reviewers. Authors may include data in support of their argument even if the data are not included in the manuscript.

Changes referring to an Editor or reviewer query regarding moving or adding references, tables, or figures should be highlighted. Deletions should be marked with strikethrough (a line drawn through the selected text, using the ab button) and highlighted. Authors should submit a highlighted clean version without using the track changes function in MS Word.

VII. PREPRINT POLICY

A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal.

KMJ allows authors to submit the preprint to the journal. It is not treated as duplicate submission or duplicate publication. KMJ recommend authors to disclose it with DOI in the letter to the editor during the submission process. Otherwise, it may be screened from the plagiarism check program–Similarity Check (Crosscheck) or Copy Killer. Preprint submission will be processed through the same peer-review process with a usual submission. If the preprint is accepted for publication, authors are recommended to update the info at the preprint with a link to the published article in KMJ, including DOI at KMJ. It is strongly recommended that authors cite the article in KMJ instead of the preprint at their next submission to journals.

VIII. COPYRIGHT AND OPEN ACCESS POLICY

Copyright

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IX. AUTHOR'S MANUSCRIPT CHECKLIST

☐ **Formatting:** Double-spaced typing in A4 or letter-size paper using 12-point Times New Roman font in an electronic file made by Microsoft (MS) Word.

☐ **Sequence:** Title page, Conflict of interest, All sources of funding, Author contributions, Abstract and keywords, Main text, (Acknowledgments), References, Tables, and Figure legends. Numbered pages and lines (from Abstract page).

☐ **Title page:** (1) The title of the manuscript; (2) author list (include ORCID); (3) names of each author's institutions and an indication of each author's affiliation; (4) the name, address, telephone numbers, and e-mail address of the corresponding author; (5) if necessary, the source of any research funding; and (6) a running title of fewer than 50 characters.

☐ **Abstract and Keywords**

- Original article (structured—background, methods, results, and conclusion—within 250 words)
- Review article (unstructured, ≤250 words)
- Case report (unstructured, ≤250 words)

Three to five keywords as in MeSH

☐ **Main text**

- Original article (introduction, methods, results, discussion)

- Review article (≤6,000 words), Case report (≤1,500 words), Editorial (≤1,000 words)

Turn on serial line numbering from the beginning of the main text.

☐ **References**

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