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順天堂醫事雑誌

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JUNTENDO MEDICAL JOURNAL

順天堂醫事雜誌

The History of *Juntendo Medical Journal*

This *Juntendo Medical Journal* has been published under the Japanese name *Juntendo Igaku* (順天堂医学) from 1964 to 2012. However, the origin of *Juntendo Medical Journal* dates back to the oldest medical journal in Japan, *Juntendo Iji Zasshi* (順天堂醫事雜誌), which had been published between 1875 and 1877 (total of 8 issues). Between 1885 and 1886, Juntendo issued a limited release of a research journal titled *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) for a total of 39 issues.

In 1887, *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) was published with the government's approval and we used to regard this as the first issue of *Juntendo Medical Journal*. Since then, *Juntendo Medical Journal* has undergone a series of name changes: *Juntendo Iji Kenkyukai Zasshi* (順天堂醫事研究会雜誌), *Juntendo Igaku Zasshi* (順天堂医学雑誌), and *Juntendo Igaku* (順天堂医学).

Now in commemoration of the 175th anniversary of Juntendo University, starting with the first volume issued in 2013 (Volume 59 Number 1), we return to *Juntendo Medical Journal*'s original Japanese title in 1875-*Juntendo Iji Zasshi* (順天堂醫事雜誌). We also reconsidered the numbering of the journal and set the first issue in 1875 as the initial publication of *Juntendo Medical Journal*. The Volume-Number counting system and the English name *Juntendo Medical Journal* started in 1955 from the January 10 issue. Although this is not our intension, we will retain the Volume-Number counting system to avoid confusion. However, Volume 59 Number 1 will be the 882nd issue, reflecting the sum of all issues to date: 8 issues of *Juntendo Iji Zasshi* (順天堂醫事雜誌), 39 issues of *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) (47 issues combined), and 834 issues from *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) in 1887 to the present.

出典：小川秀興（OGAWA Hideoki, M.D., Ph.D.）：順天堂醫事雜誌（Juntendo Medical Journal）2013；59：6-10.

本誌は昭和39年（1964年）から平成24年（2012年）末まで『順天堂医学』として刊行されてきた．しかし，その起源は明治8年（1875年）から10年（1877年）にかけて発刊された日本最古の医学誌『順天堂醫事雜誌』（計8巻）にある．さらに明治18年（1885年）から19年（1886年）まで，会員限定配本として順天堂醫事研究會の雑誌『報告』（計39集）が発行されている．

その後『順天堂醫事研究會報告』が明治20年（1887年）に官許を受けて公刊されたので，順天堂ではこれを通刊1号としてきた．以来，『順天堂醫事研究会雑誌』，『順天堂医学雑誌』，『順天堂医学』と名称を変更して刊行されてきた．

今般，順天堂が創立175周年を迎える平成25年（2013年）の59巻1号を期して，本来の名称である『順天堂醫事雜誌』と復刻し，その起源である明治8年（1875年）第1巻をもって創刊号（通刊第1号）とすることとした．従来の巻号と欧文誌名は，昭和30年（1955年）1月10日発行のものを1巻1号としており，欧文誌名もこれより付け始めたもので不本意であるが，混乱を避けるためにこれらを継承する．ただし，通刊数は明治8年（1875年）から19年（1886年）にかけて刊行された『順天堂醫事雜誌』8巻分と順天堂醫事研究會の雑誌『報告』39集，計47巻分を通巻834号に加え，59巻1号を通刊882号とした．

出典：小川鼎三，酒井シヅ：順天堂医学　1980；26：414-418.
小川秀興：順天堂醫事雜誌　2013；59：6-10.

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From the illustrator: On the day of "Hatsumode" (the first visit of the year) to Naritasan Temple, I found something interesting at a mysterious antique shop on the way home. Rabbit boy is confessing love to Rabbit girl while handing over a bouquet. I was fascinated by its fairy-tale like colors. It is the best motif for Year of the Rabbit!

Reviews

Juntendo Medical Journal
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Cutting-edge Treatment for Gynecological Malignancies

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Gynecological malignant tumors can develop in the vulva, vagina, uterus, fallopian tubes, or ovaries in the female reproductive tract. The cervix, uterine body, and ovaries are particularly common sites for malignant tumors. Surgery, radiation, and drug therapy are the main treatment modalities for gynecological cancers, with surgery being the most important of them.

We started laparoscopic surgery for uterine endometrial cancer as an advanced medical treatment in 2011 and contributed to its insurance coverage. We were able to reproduce our laparoscopic surgery more easily using the da Vinci Xi system for robotic surgery. We have now switched from laparoscopic surgery for endometrial cancer to robotic surgery and have been able to perform them safely and reliably.

In the case of cervical cancer, the results of the Laparoscopic Approach to Cervical Cancer (LACC) trial, which compared the prognosis of two groups of radical hysterectomy for early-stage cervical cancer: conventional open surgery and laparoscopic/robotic (minimally invasive) surgery, showed that minimally invasive surgery resulted in more pelvic recurrences and had a worse prognosis compared with open surgery. The trend toward minimally invasive surgery for cervical cancer has stagnated worldwide.

Ovarian cancer has few symptoms in the early stages and is often found at stage III or IV, when the cancer has spread throughout the abdominal cavity. As residual tumor after surgery correlates with prognosis in ovarian cancer, debulking surgery should be performed to achieve complete resection. Therefore, peritoneal or bowel resection is often required to remove disseminated or metastatic tumors. We also performed prophylactic salpingo-oophorectomy to prevent ovarian and fallopian tube cancers in patients with *BRCA1/2* gene variants.

The uterus and ovaries are organs necessary for pregnancy and childbirth, and cancer of the uterus or ovaries in women of childbearing age may result in infertility. Surgery and adjuvant treatment may affect marriage, childbirth, and sexual life; therefore, it is important to ensure the cure of cancer and to provide patients with treatment methods that allow them to live their lives as women.

Key words: gynecological surgery, cervical cancer, endometrial cancer, ovarian cancer, minimal invasive surgery

Introduction

Gynecological cancers are specific to women, and malignant tumors can develop in the vulva, vagina, uterus, fallopian tubes, and ovaries in the female reproductive tract, but the cervix, uterine body, and ovaries are particularly common sites. Surgery, radiation, and drug therapy are the main treatment modalities for gynecological cancers, with surgery being the most important treatment modality.

With advances in optical equipment and power sources, laparoscopic surgery is now indicated for malignant cases that were once considered difficult, and laparoscopic surgery for endometrial and cervical cancers have been covered by insurance since 2014 and 2018. In addition, robotic surgery for

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uterine endometrial cancer was covered by insurance in 2018. Robotic surgery for gynecological diseases is more common than laparoscopic surgery in the United States[1]. In our hospital, we have been actively performing laparoscopic and robotic surgeries, and we would like to introduce them here. In ovarian cancer, postoperative residual tumor correlates with prognosis, so debulking surgery should be performed with the aim of achieving complete surgery with no visible residual tumor. Therefore, peritoneal and bowel resection are often required to remove disseminated or metastatic tumors as much as possible, which is not minimally invasive. In our department, we perform complete resection of ovarian cancer without complications, in cooperation with the departments of colorectal surgery, hepatobiliary surgery, and urology. We also introduce the latest surgical treatments for gynecological cancer, such as prophylactic salpingo-oophorectomy, to prevent ovarian and fallopian tube cancers in patients with *BRCA1/2* gene variants.

Uterine endometrial cancer

Endometrial cancer is a cancer that develops in the endometrium of the uterus. The occurrence site and cause are different from those of cervical cancer of the uterus. The number of cases of endometrial cancer began to increase in the late 40s around the time of menopause and is most common in women in their 50s and 60s. As it is difficult to accurately diagnose endometrial cancer, which is found in the body of the uterus, surgery is performed after estimating the clinical stage based on preoperative imaging, and the pathological stage is classified again after surgery. The risk of recurrence was assessed after surgery. Based on the stage and risk of recurrence, it is decided whether adjuvant treatment is necessary after surgery. Surgery is the first choice of treatment for endometrial cancer, regardless of the advanced stage. However, the type of surgery performed depends on its stage. If the risk of surgery is high owing to advanced age, serious diabetes, heart disease, severe obesity, or if the cancer has already spread throughout the body and surgery is not expected to be effective, chemotherapy, radiation therapy, or palliative care may be used.

In stage I cases, in which the cancer is presumed to be confined to the uterine body only, the standard procedure is a total hysterectomy, in which the entire uterus is removed, and a bilateral salpingo-oophorectomy, in which both the ovaries and fallopian tubes are removed. Depending on the histological type and degree of invasion into the myometrium, pelvic or paraaortic lymph nodes may be removed.

Until 2010, all cases of endometrial cancer were treated with open surgery in our hospital. The abdominal incision was a midline incision at the level of the umbilicus or up to the xiphoid process. This is a highly invasive surgery. At that time, there was little evidence of minimally invasive surgery (MIS) for gynecological malignancies in Japan. We started laparoscopic surgery for early-stage endometrial cancer because we thought that if we could reproduce the open surgical technique using laparoscopy, we could establish a standard procedure that was safe and curative while maintaining surgical completion and accuracy. The indications for laparoscopic surgery were G1 or G2 endometrioid carcinoma with myometrial invasion ≤1/2, and the basic surgical techniques were total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. The instruments used were standardized. To prevent tumor dispersal, a uterine manipulator was not inserted, and the uterus and lymph nodes were removed from the body in a bag. The results showed that laparoscopic surgery prolonged the operation time compared with open surgery but decreased the amount of blood loss, hospital stay, and visual analogue scale score on postoperative day 1. There were no significant differences in progression free survival and overall survival[2]. The results contributed to the insurance coverage of laparoscopic surgery for uterine endometrial cancer.

However, laparoscopic surgery requires more time to master than open surgery. This is because it is a magnified view, and it is necessary to visualize the three-dimensional (3D) in a two-dimensional view. In addition, eye-hand coordination is required. In robotic surgery, once surgeons are accustomed to the magnified vision, robotic surgery provides 3D vision, and forceps can be moved freely like in open surgery[3,4].

Table 1 shows a comparison of short- and long-term outcomes, invasiveness, learning curve, cost

Table 1 Benefit for minimally invasive surgery in endometrial cancer

	Open surgery	Laparoscopic surgery	Robotic surgery
Short term outcome	○	○	○
Long-term outcome	○	○	○
Less invasiveness	△	○	○
Learning curve	○	△	○
Cost effectiveness	△	○	△
Easy accessibility	○	○	○

The meaning of ○ is equivalent to the others, △ means inferior to others

effectiveness, and easy accessibility of open, laparoscopic, and robotic surgery in early endometrial cancer surgery[5–9]. Easy accessibility was further improved by using the Da Vinci Xi system. In 2018, robotic surgery for uterine cancer was covered by the insurance. Eighty-two cases (41 robotic and 41 laparoscopic surgeries) of total hysterectomy and bilateral adnexectomy with MIS for uterine cancer between 2019 and 2020 were reviewed. Robotic surgery had similar blood loss and complication rates as those of laparoscopic surgery. Robotic surgery shortened the operating time compared to laparoscopic surgery. Our laparoscopic surgery for endometrial cancer can be more easily reproduced using the da Vinci Xi system. We have now switched all laparoscopic surgeries for endometrial cancer to robotic surgery and have been able to perform them safely and reliably.

Cervical cancer

Cervical cancer occurs in the cervix, which is the entrance point to the uterus. Cancer develops near the junction of squamous and columnar cells that line the cervical surface. It is mainly classified as a squamous cell carcinoma or adenocarcinoma. Cervical cancer is most common in women in their late 30s and 40s. It is caused by human papillomavirus (HPV). Persistent infection with highly carcinogenic HPV causes dysplasia (precancerous lesions), and some of these lesions become cancerous over a period of 5–10 years, progressing from mild-to-moderate to severe dysplasia. In the case of mild or moderate dysplasia, the patient is followed-up regularly, and in the case of severe dysplasia or carcinoma in situ, cervical conization is performed. When further carcinogenesis develops, cervical cancer is classified into four stages: stages I, II, III, and IV. Cervical conization that can preserve fertility can be performed if the cancer is carcinoma in situ, in which the cancer remains in the epithelial cells, and microinvasive carcinoma (stage IA), in which the cancer invades the stroma on a millimeter scale.

Stage IA to IIb cervical cancer is operable. However, depending on the stage, there are several methods for uterine removal. Radical hysterectomy is one of the most difficult gynecological surgeries. MIS was performed for both cervical and endometrial cancer. However, the LACC trial published in 2018 changed the trend toward MIS. In a 13-country comparative study, the authors compared the outcomes of two groups of radical hysterectomies for early-stage cervical cancer: conventional laparotomy (open) and laparoscopic/robotic surgery (MIS). The results showed that MIS resulted in greater pelvic recurrence and worse prognosis than open surgery[10]. In a retrospective study, MIS had a poorer prognosis than open surgery[11, 12]. The trend toward MIS for cervical cancer has been stalled worldwide.

In the case of local recurrence after radiotherapy for cervical cancer, surgical therapy is now the treatment of choice if there are no distant or lymph node metastases. In such cases, total pelvic exenteration (TPE) or anterior or posterior segment excision is a radical surgical procedure that removes organs, including the bladder, urethra, rectum, anus, vagina, uterus, fallopian tubes, ovaries, and vulva. TPE has become safer than in the past, with a mortality rate of approximately 0.5 to 2%[13–15]. However, postoperative complications in gynecology are as high as 67%[15].

Four TPEs were performed at our hospital between 2010 and 2021. The median age of the patients was 59 years. The indicated diseases were cervical cancer recurrence (all after concurrent

chemoradiotherapy) in three patients and first vaginal sarcoma in one patient. The mean operative time was 667±80 min, and the mean blood loss was 3,216±2,820 mL. All patients underwent laparotomy and transperineal surgery, which was performed jointly with the Department of Colorectal Surgery and the Department of Urology. All patients required blood transfusions, and the only complication of grade III or higher according to the Clavien–Dindo classification was grade IIIa bowel obstruction. The mean length of hospital stay was 31 (±7) days. All patients had negative surgical margins, three were disease-free, and one was alive. As a surgical innovation, we previously operated safely on a giant myoma by using a balloon catheter to block the blood flow[16]. As an application of this technique, intraaortic balloon occlusion was used to safely perform the surgery. However, even without serious complications, mental acceptance of double stoma requires time; therefore, it is essential to provide mental care from multiple professions from an early stage.

Ovarian cancer

Ovarian cancer has few symptoms in the early stages. The organs below the diaphragm, including the uterus, ovaries, stomach, and intestines, are covered by peritoneum. Ovarian cancer is similar to cancers arising in the fallopian tubes and peritoneum; therefore, these cancers are treated together as same. Various tumors can occur in the ovaries. Depending on the tumor location, they are classified into three main categories: (1) epithelial tumors, (2) sex cord stromal tumors, and (3) germ cell tumors. Tumors are further divided into (1) benign, (2) borderline malignant, and (3) malignant. Epithelial tumors are the most common type of ovarian tumors, accounting for approximately 90% of all malignant ovarian tumors. Generally, the term ovarian cancer refers to malignant epithelial tumors.

Ovarian cancer is one of the most difficult cancers to detect early due to a lack of symptoms and appropriate screening methods. More than 40% of ovarian cancers are found in advanced stages III and IV.

If ovarian cancer is suspected, surgery is often the first step at an advanced stage. Intraoperative pathology will determine whether an ovarian tumor is benign or malignant. In the case of borderline malignancy or malignancy, both ovaries, uterus, and omentum are removed. If the cancer is scattered in the abdomen at the time of surgery (peritoneal dissemination), a tumor resection surgery is performed to remove as much of the cancer as possible. For ovarian cancer, the less tumor remains after surgery, the better is the prognosis[17]. Therefore, surgery should be performed with maximum debulking with the goal of achieving a complete surgery, in which there is no gross residual tumor. Peritoneal or partial bowel resection is often required to remove disseminated or metastatic lesions. In our hospital, the percentage of patients with ovarian cancer who underwent intestinal resection was 7.1% (43 cases) between 1995–2011 and 57 cases (10.7%) between 2012–2020, and the percentage has been increasing gradually. The surgical strategy for ovarian cancer with pelvic peritoneal dissemination at our hospital is shown in Figure 1. The abdominal cavity was observed after laparotomy. We evaluated whether all the tumors could be removed. If the cancer is not resected, chemotherapy should be administered followed by interval debulking surgery. If only pelvic peritoneal dissemination was present, it could be removed. If bladder or intestinal tract invasion is observed, partial resection of the bladder, sigmoid colon, or rectum is performed. If there is no involvement of the bladder or intestinal tract, the peritoneum is resected. Usually, leakage of anastomosis occurs in 2.8–30% of the cases, 75% of which occur at the rectal anastomosis site[18]. The rate of anastomotic leakage in ovarian cancer is 1%. Compared to colorectal cancer surgery, there is no need to cut the root of the blood vessel; therefore, the complication rate is low. We performed complete resections safely and without complications, with the cooperation of the departments of colorectal surgery, hepatobiliary surgery, and urology.

Genetic factors are strongly associated with approximately 10% of the ovarian cancers, and pathological variants of *BRCA1* or *BRCA2* predispose ovarian and breast cancers. Risk-reducing salpingo-oophorectomy reduces the risk of developing ovarian cancer and the overall mortality in women with *BRCA 1/2* genetic variants[19–21] and is recommended in the guidelines.

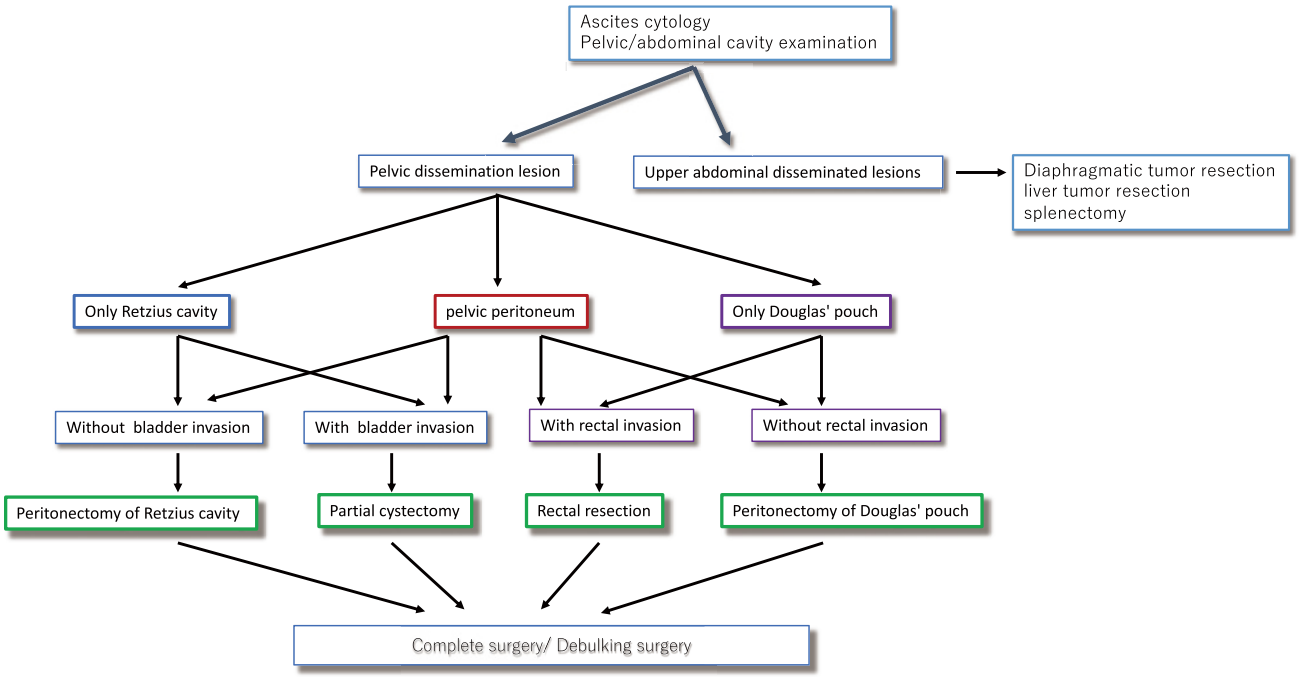

Figure 1 Strategy for ovarian cancer surgery
Observe the peritoneal cavity after collecting ascites. If the tumor is in the upper abdomen, it is evaluated whether it can be completely removed. If the tumor is only in the pelvis, it can be completely removed following the procedure.

Conclusion

Surgery is one of the most important treatments for gynecological cancers. Surgery is the most efficient way to remove cancer cells; however, it is also invasive. The choice of surgery should be based on patient's age and general condition. In addition, the uterus and ovaries are organs necessary for pregnancy and childbirth, and cancers of the uterus or ovaries in childbearing age may result in loss of fertility. It is important to perform surgery that preserves the possibility of fertility. Surgery and subsequent treatment may affect marriage, childbirth, and sex life; therefore, it is important to provide patients with treatment methods that allow them to face their "womanhood" while ensuring the cure of cancer.

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Author contributions

YT wrote and approved the final manuscript.

Conflicts of interest statement

The author declares that there are no conflicts of interest.

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Reviews

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Current Neurosurgery

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Neurosurgery is based on neuroscience, physiology and medical physics. Therefore, neurosurgery has also developed along with discoveries and innovations in these fields. The present article outlines the areas of neurosurgery and their development until 2022.

Technology for the preservation of the central nervous system and cranial nerve function has made remarkable progress through the integration of diagnostic imaging and functional evaluation capabilities.
Endovascular treatment strategies of cerebrovascular disorders have also progressed. The procedures have not only shifted from craniotomy to endovascular catheterization, but the devices used in these procedures have also changed.

In addition to these traditional disease treatment strategies/techniques, neurosurgical techniques have recently been used in surgical procedures to improve quality of life. Epilepsy, is one of the diseases that does not significantly have a direct impact on life outcomes. However, epilepsy patients find it difficult to reintegrate into society. In epilepsy, seizure management is important, and some subgroups of patients can be better treated using surgical intervention than by using pharmacotherapy. In addition, the treatment of dementia due to idiopathic normal pressure hydrocephalus can be improved by surgical management of the cerebrospinal fluid. Neurosurgical intervention can help diseased patients reintegrate into society, which is difficult without treatment.

Even in these disease groups, surgical intervention may have irreversible consequences. Therefore, its implications should be decided based on universal scientific evidence.

Key words: neurosurgery, brain tumor, endovascular surgery, functional surgery

Introduction

Neurosurgery is a branch of neuroscience in which the surgeons aim to surgically treat diseases of the central nervous system (CNS). The CNS includes the brain and spinal cord, and the peripheral nerves that emerge from them. CNS surgeries must be performed only after they are validated on the basis of scientific, physiological, and physical theory.

Juntendo University has a Neurosurgery department that is operating for a long time and has dealt with complicated cases. One of the most significant examples is of Susumu Sato, the third president of Juntendo, who removed a depressed bone fragment and bullet to save a civil war survivor and also drained a brain abscess. This occurred approximately 100 years before neurosurgery was defined as a medical specialty in Japan.

Presently, the field has advanced and is progressing increasingly. The surgery performed by Dr. Sato previously can now be performed with less effort. The article provides a review of the recent trends in neurosurgery with focus on current challenges.

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The surgical removal of brain tumors

Brain tumor surgery is a technique that reflects recent technological innovations. Brain tumors are not necessarily the term for tumors of the brain parenchyma but often refer to intracranial neoplasms in general. Thus, it also includes lesions outside the brain parenchyma and neoplastic lesions in the pituitary gland and other organs.

For tumors located in the midbasal region of the skull (such as the pituitary gland), transnasal endoscopic surgery has been developed to reach the lesion through the nasal cavity that does not require craniotomy[1]. Currently, the standard surgical approach for craniopharyngiomas and pituitary adenomas treatment is transnasal surgery. Additionally, this novel technique can be applied for the treatment of small meningiomas, chordomas of the clivus, and small lesions of the medial orbit[2]. Previously, skull base surgery required knowledge of the anatomy of the skull base bone from above, as glimpsed through the space between the brain. Today, the skull base is viewed from below, and the knowledge required is changing.

Two major evolutions have taken place in the treatment strategies of parenchymal brain tumors: intraoperative neurological function preservation techniques. Since many parenchymal brain tumors are not benign, they cannot be curatively removed as they can infiltrate into functional brain. This is the reason why removal of the entire tumor from a functioning brain, regardless of its invasiveness, is detrimental to prognosis. Therefore, advanced methods are being developed to identify critical functional areas in preoperative images before surgery. Furthermore, it is now possible to perform intra-operative MRI with the cranium open and to use the information in real time while removing the tumor[3]. This information is shared not only with the surgeon, but also to the medical staff. Therefore, current operating rooms resemble information processing rooms with countless monitors displaying various parameters as per the requirement (Figure 1).

The second is the diagnosis of brain parenchymal tumors. It is well-established that analysis of molecular biological characteristics of tumor cells help in accurate prognosis compared with conventionally used histopathology analysis (Table 1)[4]. Thus, histopathology is no longer sufficient for the classification and diagnosis of brain parenchymal tumors. Many of these analyses are costly and require special techniques; therefore, it is essential to collaborate with research institute for analysis[5]. In

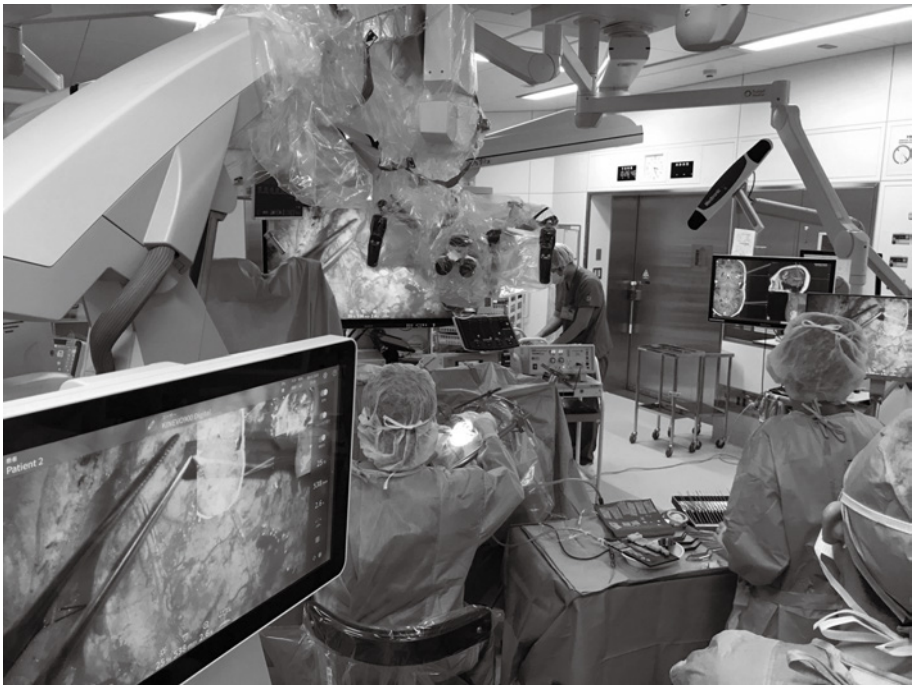

Figure 1 An operating room where brain tumor resection is performed. A number of monitors display various parameters to show the patient's functional preservation status.

Table 1 The list of diffuse gliomas in the 2021 World Health Organization Classification of Tumors of the Central Nervous System

Adult-type diffuse gliomas
Astrocytoma, *IDH*-mutant Oligodendroglioma, *IDH*-mutant and 1p/19q-codeleted Glioblastoma, *IDH*-wildtype
Pediatric-type diffuse low-grade gliomas
Diffuse astrocytoma, *MYB* or *MYBL1*-altered Angiocentric glioma Diffuse low-grade glioma, *FGFR*-altered Polymorphous low-grade neuroepithelial tumor of the young Diffuse low-grade glioma, *BRAF* V600E-mutant
Pediatric-type diffuse high-grade gliomas
Diffuse midline glioma, H3 K27M-mutant Diffuse hemispheric glioma, H3 G34-mutant Diffuse pediatric-type high-grade glioma,H3 wildtype and *IDH* wild type Bithalamic glioma, *EGFR*-mutant Infant-type hemispheric glioma, H3-wildtype

Modified from reference No.4.

the future, there will be a need for the development of treatments based on these classifications.

The procedure for vascular lesions

The changes observed in the treatment strategies of cerebrovascular disorders are as follows. First, transvenous thrombolysis was introduced for cerebral infarction or stroke cases. This therapy is designed to dissolve the thrombus as soon as possible after the onset of stroke, before endothelial damage progresses, thereby allowing the vessel to recanalize. Statistically, this has been shown to dramatically reduce stroke mortality. Furthermore, advances in cerebral infarction treatment have led to the development of devices that aspirate and retract thrombi from within blood vessels in cases of thromboembolization of major vessels. Mechanical thrombectomy, the physical removal of thrombi, is being introduced into the emergency settings. Since emboli in major cerebral vessels can disrupt a large area of the brain, removal of the thrombus can minimize the area of ischemia and improve functional prognosis.

In addition, many treatments for vascular lesions (cerebral aneurysms) have shifted from opening the skull and fissure of the brain to using intravascular catheters to reach the lesions[6]. Technological innovations in cerebral aneurysms, in particular, have been remarkable. The conventional method of preventing aneurysm rupture, which is filling the aneurysm with multiple coils, has been replaced by the clinical use of a flow-diverter stent, which rectifies blood flow[7]. This stent is inserted in the parent artery where the aneurysm has occurred, thereby preventing turbulent flow within the aneurysm. In addition, devices that can prevent re-rupture of a ruptured aneurysm such as a stent of a special shape that matches the diameter of the aneurysm, are also being used[8].

Functional surgery

The main targets of neurosurgery are traumatic injuries, vascular disorders, and tumors, which, if untreated, can be fatal or disabling. This is because the nervous system, especially the CNS is vulnerable to external stress and it gets irreversibly damaged. Surgical treatment is considered to halt the progression of central nervous system disorders.

Recent advances in neuroradiological evaluation have made it possible to image intracranial and internal nerve conditions with considerable accuracy[9]. This allows us to safely reach the site of injury and even depict temporary dysfunction due to compression or malalignment without causing major damage.

The field that has developed in this context is functional neurosurgery. It is a medical treatment that uses surgical procedures to improve the quality of life of patients affected with chronic illnesses that do not lead to death.

Epilepsy

Epilepsy surgery is a representative of these treatment strategies. The prevalence of epilepsy is estimated to be 1 in 100 patients[10]. More than 70% of these patients can manage their seizures and achieve social cure with medical treatment such as antiepileptic drugs. However, approximately 30% of the patients may require surgical treatment[11]. Specific surgical procedures in this case include removal of the seizure focus to prevent of the progression of seizures. For example, when the seizure source is located in the medial temporal lobe, so-called generalized tonic seizures are secondary to complex partial seizures that are often awake but difficult to communicate with. This type of epilepsy is easily overlooked and requires special electroencephalography. In addition, because of the unique location of the medial temporal lobe, the rate of seizure control with antiepileptic drugs is significantly lower than that of other types of epilepsy involving the frontal lobe of the brain[12]. The removal of the epileptic focus is the first-line treatment for this disease. Epileptic foci are scattered throughout the cerebrum on one side in epilepsy, causing secondary generalization that spreads seizures to the healthy brain via brain fibers. Weaning the fibers may reduce generalization and facilitate seizure management. In this case, dissection of the commissural fibers of the brain is indicated[13].

In addition, patients who are difficult to manage even with such surgery may be managed using vagus nerve stimulation, which is electrical stimulation of the cervical vagus nerve. In this procedure, electrodes are wrapped around the cervical vagus nerve and connected to a generator with adjustable electrical stimulation implanted in the chest to suppress severe seizures[14].

Patients who have had difficulty managing their epilepsy with medication and have had difficulty finding regular employment in their lives often return to normal life after undergoing epilepsy surgical procedures.

These surgeries have irreversible consequences on the central nervous system; therefore, careful determination of indications and preoperative analysis are important.

Idiopathic normal pressure hydrocephalus

With recent medical advances, society is aging. Dementia is a disease that has attracted considerable attention. To date, no effective treatment for dementia has been found. However, some patients show mild cognitive symptoms, which occurs in a small percentage of patients due to hydrocephalus. This disorder is idiopathic with normal pressure hydrocephalus. Affected individuals present with mild attention and memory deficits, a unique wiggly gait, mild urinary urgency, and incontinence. Neurological symptoms can be ameliorated by draining cerebrospinal fluid through a tube into the abdominal cavity.

However, until now, this symptom has been the only diagnostic criterion, but our research group has identified a special protein that precipitates in the cerebrospinal fluid and found a method to diagnose the disease using this protein as a biomarker[15]. In addition, we pointed out that the hydrocephalus-like appearance of enlarged ventricular diameters in this disease may be due to directional abnormality of ciliary motility in the ventricular ependyma[16]. As a result, the diagnosis is now easier and patients can be expected to improve with the surgical tube placement. Patients who have achieved improvement in gait disturbance are pleased with the outcomes, proving that surgical treatment improves their quality of life.

The other indications

Surgical treatment may have better outcomes than medical treatment. In cases such as hemifacial spasms and trigeminal neuralgia, where the symptoms are clearly caused by arterial compression of the causative nerve, surgical treatment is the only option. However, with advances in drug development, involuntary facial muscle movements and neuropathic pain caused by this compression can now be managed through drug administration, making drug therapy is the first choice. However, patients can be allergic to these drugs and prolonged use can render the treatment ineffective. Hence, there is a growing preference, both economically and psychologically, for surgical relief of the underlying cause of the compression phenomenon, rather than continuation of drug therapy[17].

Recent image analysis technology has made it

possible to clearly delineate the positional relationship between nerves and blood vessels. In addition, the ease of identification of surgical pathways to lesions has dramatically improved the safety of surgery. This is one of the reasons why surgery and drug therapy can now comparable.

Other patient groups, such as those of Parkinson's disease and spinal cord disease, have better outcomes and prognoses with surgical intervention than with pharmacotherapy[18]. Functional surgeries are now comparable to conventional treatment strategies.

Conclusions

The present article compares the traditional (150 years ago) and contemporary neurosurgery methods (2000–2022). The field is advancing constantly. Although novel neurosurgery techniques are being developed, they are based on the basic principles of medical physiology and physics. The field will keep on developing along with evidence-based medicine. I believe that this article is the first one to provide a comprehensive information on both traditional and modern neurosurgeries.

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Author contributions

AK planned this manuscript, collected the appropriate literature information, and drafted the manuscript. AK also reviewed and approved the final version of the manuscript for publication.

Conflicts of interest statement

The author declares that there are no conflicts of interest.

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Reviews

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The Latest Treatment for Head and Neck Cancers: Transoral Robotic Surgery and Photoimmunotherapy

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Remarkable progress has been achieved in head and neck surgery in recent years. Transoral robotic surgery (TORS) is becoming popular worldwide for the removal of less invasive tumors. TORS is used especially for oropharyngeal cancer and is minimally invasive, with a short treatment time and minimal postoperative dysfunction. The procedure is performed by inserting one endoscope and two robotic arms. The robotic arm has a 360-degree movable tip, which enables fine manipulation, even in narrow oral cavities. The endoscope also provides three-dimensional images and enables the surgeon to get close to the operative site, making it possible to check for small blood vessels and other objects while performing the operation.

Photoimmunotherapy is a new treatment for distant metastasis or recurrent head and neck cancers not indicated for surgery or radiotherapy. Treatment requires the administration of a dye, IR700, one day before the procedure. This dye disrupts cell membranes when exposed to near-infrared (NIR) radiation. To deliver this dye specifically to the tumor, an antibody drug against the epidermal growth factor receptor, which is expressed relatively specifically in tumors, is used. This treatment has a strong anti-tumor effect and the tumor shrinks relatively quickly. However, because NIR irradiation is required, the lesion must be within the infrared irradiation range. In addition, because of rapid shrinkage of the tumor, post-treatment tissue defects are serous complication, and tumor invasion into the carotid artery are contraindications due to the risk for major hemorrhage caused by tumor shrinkage.

Key words: head and neck cancer, trans oral robotic surgery, photo immune therapy

Introduction

The field of otorhinolaryngology is diverse and includes the disciplines of otology, rhinology, and head and neck surgery. Head and neck surgery addresses tumors that occur in the head and neck region and is a field that has witnessed remarkable progress in recent years. Radiotherapy and surgery using external incisions are conventional curative treatments for head and neck cancers. In addition, drug therapy is commonly used in cases of distant metastasis or recurrence, although it is difficult to achieve complete cure using drug therapy alone. In the present article, we introduce and discuss robotic surgery and photoimmunotherapy as the latest treatments for head and neck cancers.

Transoral robotic surgery

Recent advances in endoscopic techniques, especially the introduction of narrowband imaging (NBI), have made it possible to detect pharyngeal cancer at an earlier stage than in the past. NBI is a pioneering technology developed in the field of gastrointestinal endoscopy that has been recently

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applied to the head and neck region. NBI is an optical imaging enhancement technology that depicts capillaries in the superficial layer of the mucosa in brown and those in the submucosal tissue in blue-green on a monitor, thus enabling identification of lesion(s) that develop from capillaries characteristic of superficial cancer.

Efforts are now being made to perform less-invasive resection of cancers detected at an early stage using these techniques, and robots can now be used to perform less-invasive resection(s). Cases that previously required external incisions or radiotherapy can now be treated less invasively and in a shorter period by removing the cancer transorally. The conventional external incision approach results in an incision wound on the neck, which is inferior in terms of cosmetic appearance. In addition, the neck wound heals with scarring, causing postoperative discomfort and neck contracture. In addition, postoperative swallowing function is impaired due to scar contracture and the resection of muscles necessary for swallowing. Radiotherapy is an alternative to the external incision approach; however, it is also associated with decreased quality of life after treatment due to scarring of cervical tissues caused by radiation injury, which results in impaired swallowing function and salivary secretion. However, when tumors are removed transorally using a robot, surgery can be performed without incisions in the neck, which is preferred in terms of esthetics, and contracture caused by manipulation(s) of the neck can be prevented. In addition, because surgical manipulation is limited to the area around the resection site, postoperative functional deterioration due to scar contracture and muscle dehiscence can be minimized. In actual clinical practice, patients can be discharged from hospital relatively early (approximately one week after surgery) and, although some decline in swallowing function may occur, it can be minimized[1, 2]. A "big data" analysis by the United States National Cancer Database reported that the advantages of TORS included low rates of positive resection margins and postoperative chemoradiotherapy[3], and that TORS significantly prolonged overall survival compared with other modalities in human papilloma virus-positive oropharyngeal cancer[4]. Sano et al. reported a lower rate of positive margins with TORS than with other transoral resection modalities such as transoral video surgery and endoscopic laryngo-pharyngeal surgery[5]. Thus, diverse evidence supporting TORS has accumulated; however, not all head and neck cancers are indications for the procedure. Nevertheless, the lateral and anterior walls of oropharyngeal cancers are considered to be good indications. TORS has been widely used in the United States and Europe, and Japan was somewhat late in introducing robotic surgery to this area. However, insurance has covered TORS in Japan since April 2022, and the number of facilities capable of performing the procedure is gradually increasing.

TORS is performed by inserting a camera and two robotic arms (three in total) through the mouth. The robotic arm has a 360-degree movable tip, which enables detailed manipulation, even in the narrow oral cavity (Figure 1). The robotic arm is equipped with an anti-shake function such that, even if the surgeon's hands shake on the console, the robotic arm will not shake. The robot arm is also equipped with a scale function, so that the actual robotic arm moves only 1 cm when the surgeon moves his hand 5 cm; this scale can be set to 1:3 or 1:5. These features enable more precise manipulation. In addition, the endoscope provides high-quality three-dimensional images and affords the surgeon close access to the operative site, making it possible to safely proceed with the procedure while confirming the presence of small blood vessels. An important point when performing surgery is the development of a good surgical field using a mouth gag. Recently, new and improved apertures have been introduced to provide a better surgical environment. One disadvantage of robotic surgery is that the robotic arm does not have a sense of touch; as such, it is not possible to palpate the hardness of tissue, and the three arms are inserted into the narrow oral cavity; therefore, it is necessary to operate the arms carefully to avoid interference among them.

Photoimmunotherapy

Photoimmunotherapy is a new treatment method that was conditionally approved in Japan in September 2020. It is indicated only for head and neck cancers in patients with recurrent or metastatic disease and for whom none of the existing

Figure 1 A: The surgeon operates remotely from a console. B: Three robotic arms are inserted orally to perform the operation. An assistant provides support near the patient.

treatments, such as radiation or surgery, are indicated. The treatment mechanism is described as follows. A dye, IR700, which causes a chemical reaction when irradiated by near-infrared radiation (NIR), is used to damage cell membranes. This dye is administered intravenously to the patient before NIR irradiation. When this dye is exposed to light, it becomes insoluble and damages cell membranes, thereby destroying cancer cells. To make the treatment more effective, the dye must specifically bind to cancer cells and not to normal cells. To achieve this, cetuximab, an antibody against the epidermal growth factor receptor (EGFR), which is highly expressed in head and neck cancer cells, is combined with the dye and administered. This makes it possible to specifically target and bind the dye to cancer cells without binding to normal cells. Then, irradiation with NIR, which causes a reaction with the dye, causes the dye to bind to the surface of cancer cells, react, and destroy them[6-8] (Figure 2). The day before treatment, a drug containing IR700 combined with an anti-EGFR antibody is administered intravenously. Because the drug can react when exposed to light at this time, it is handled under a light shield. On the day of the procedure, the patient is transferred to the operating room for NIR irradiation of the tumor under general anesthesia; however, during this time, the dye will react if the patient is exposed to light. Therefore, the patient is transferred under a light shield (Figure 3) and the operating room is kept dark. There are two methods for irradiating lesions using NIR: frontal and cylindrical. A frontal diffuser is a method in which light is irradiated from the front as if shining a flashlight. The cylindrical diffuser is a method in which a needle is inserted into the tumor, and an optical fiber is inserted into the needle to emit light from the inside (Figure 4). Irradiation is performed by skillfully combining these two methods, considering the extent and thickness of the lesion. This therapy has a high antitumor effect on cancer cells, and the

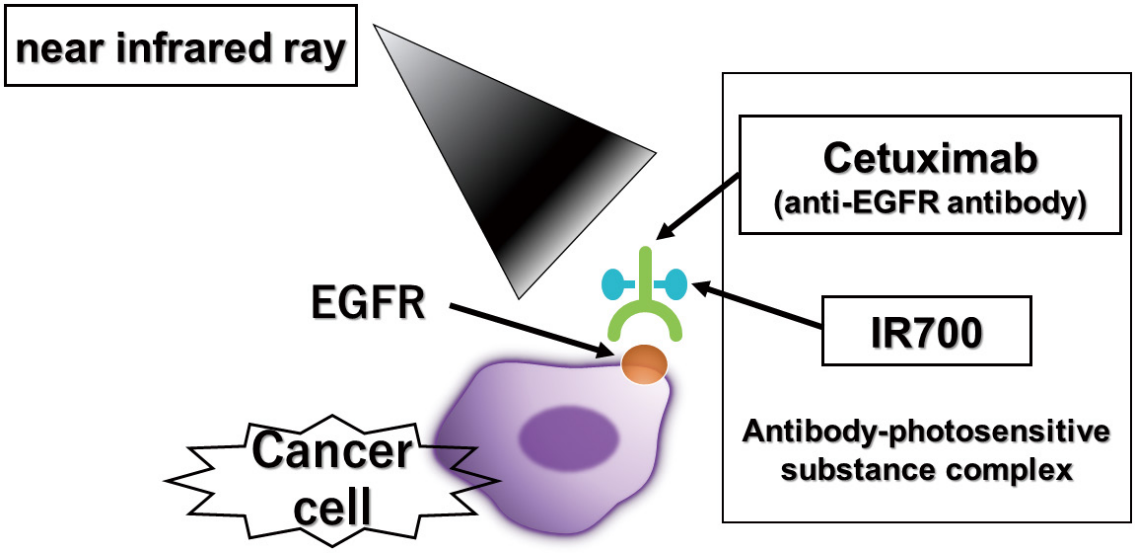

Figure 2 Mechanism of photoimmunotherapy

Figure 3 A: The drug needs to be covered with a shield to prevent exposure to light. B: The patient is transported to the operating room under a cover to prevent exposure to light.

tumor often shrinks relatively quickly; however, tissue defects due to tumor shrinkage are a major problem. In addition, if the tumor has invaded the carotid artery, treatment is contraindicated due to the risk for major bleeding caused by tumor shrinkage. The conditions for this treatment are that the tumor must have a relatively specific target—such as EGFR—to enable the dye to bind to the tumor while bypassing normal areas, and that the tumor must be located in an area that can be irradiated with NIR. For these reasons, as mentioned above, head and neck cancer is a current indication for treatment[9]. Research and development of new methods, such as the search for molecular targets to bind dyes specific to cancer cells in other types of cancers and NIR irradiation from the tip of an endoscope, are currently underway, and it is anticipated that this technology will be expanded to other areas in the future.

In addition to the direct destruction of tumors, this therapy also has other potential effects. More specifically, it enhances immunity against tumors. Conventional surgery, radiotherapy, and chemotherapy all exert anti-tumor effects; however, there is concern that the invasiveness of surgery and the side effects of treatment may reduce the physical strength of the patient. While photoimmunotherapy requires general anesthesia, the burden on the

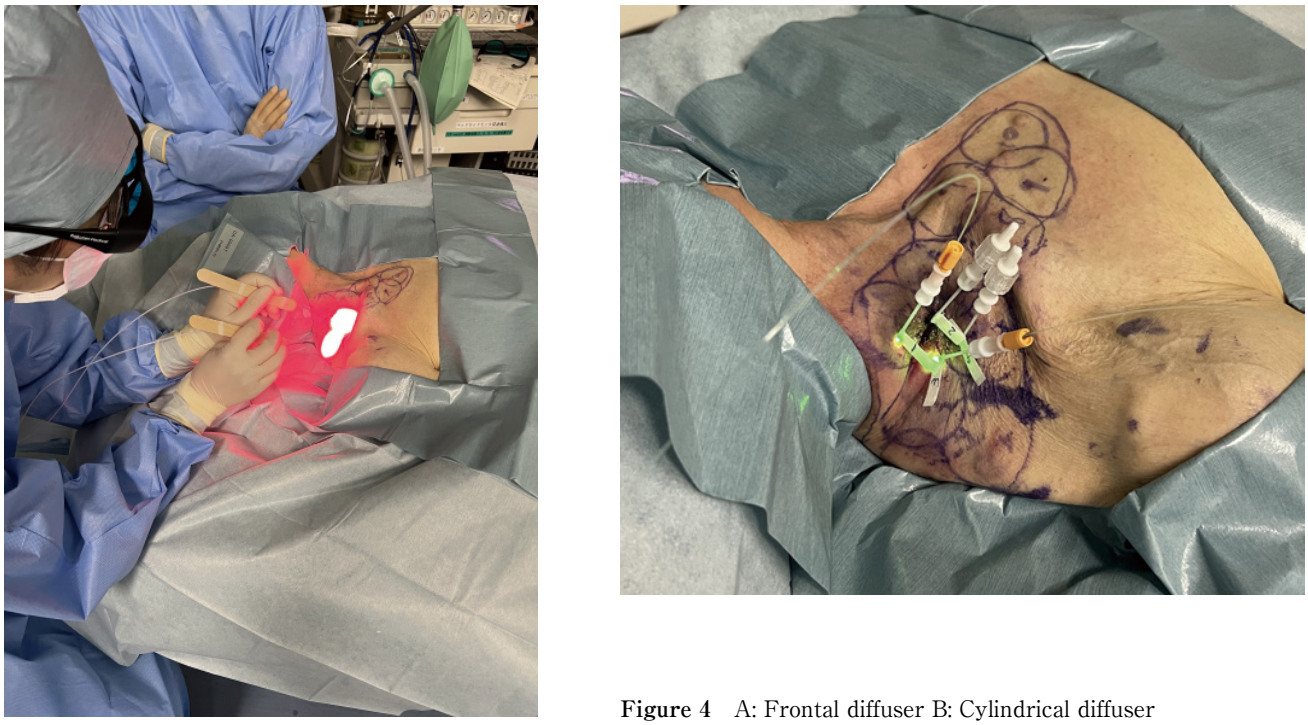

Figure 4 A: Frontal diffuser B: Cylindrical diffuser

patient is much less than that of conventional therapies. Tumor cells are destroyed without damaging the surrounding tumor tissue; as such, undamaged tumor antigens are dispersed from the destroyed tumor cells into the body. Tumor antigens are recognized by dendritic cells and other cells, which potentially enhance the patient's own tumor immunity. In turn, this enhancement of tumor immunity may have an abscopal effect, reduce the size of untreated distant metastatic lesions and prevent recurrence after treatment. Therefore, the treatment is referred to as "photoimmunotherapy". Currently, however, there are no clear data supporting such effects in clinical practice, although further evidence is anticipated to be accumulated in the future. Methods, such as combining therapy with existing immune checkpoint inhibitors, such as nivolumab and ipilimumab, to further enhance tumor immunity for cancer treatment, are being investigated. New developments are anticipated in the future, such as the use of this method in other therapies and other aspects of treatment[10].

Conclusion

Various new treatments have been developed and introduced in the field of head and neck cancer. This has led to improved prognosis and minimally invasive treatment. Further advances and development are anticipated in the future.

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Author contributions

FM drafted the manuscript. FM read and approved the final manuscript

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Abstract

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A Skin-derived Antimicrobial Peptide Derived from Insulin-like Growth Factor-binding Protein 5 (AMP-IBP5) as Therapeutic Candidate for Psoriasis

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Key words: psoriasis, antimicrobial peptide, AMP-IBP5, therapy

Antimicrobial peptide derived from insulin-like growth factor-binding protein 5 (AMP-IBP5) not only displays antimicrobial activities against invading pathogens but also has a wide range of immunomodulatory properties. In contrast to various antimicrobial peptides (AMPs) such as human β-defensins, cathelicidin LL-37 and S100A7 that are upregulated in psoriasis, insulin-like growth factor-binging protein 5, the parent protein of AMP-IBP5, is downregulated in psoriatic skin tissues. Psoriasis is an inflammatory skin disease characterized by epidermal hyperplasia, erythematous plaques, abnormal epidermal differentiation, and neutrophil infiltration into the epidermis. Although several AMPs have been implicated in the pathogenesis of psoriasis, the role of AMP-IBP5 remains unknown. Therefore, we aimed to investigate the effects of AMP-IBP5 in the pathogenesis of psoriasis using imiquimod-induced psoriasis-like mouse model and examined the underlying molecular mechanism.

Following subcutaneous administration of AMP-IBP5 into the psoriatic mice, we observed a remarkable reduction of dry scales and plaques, epidermal thickness, hyperkeratosis, parakeratosis, hyperplasia of dermal vessels and neutrophil infiltration in psoriatic mice compared to normal mice. Consistently, AMP-IBP5 administration markedly suppressed the expression of keratinocyte differentiation markers, including involucrin and loricrin, inflammatory cytokine tumor necrosis factor-α, antimicrobial peptides (cathelicidin and S100A proteins), and various angiogenesis factors from the psoriatic lesional skin. To clarify the molecular mechanism by which AMP-IBP5 alleviates psoriasis symptoms, we focused on low-density lipoprotein receptor-related protein 1 (LRP1), which regulates inflammatory responses and keratinocyte differentiation. The expression of LRP1 was noticeably decreased in the lesional skin of patients with psoriasis compared to that nonlesional or normal skin tissues, suggesting that dysregulation of LRP1 in the epidermis may be involved in the pathogenesis of psoriasis. Interestingly, administration of LRP1 antagonist, receptor-associated protein (RAP), exacerbated psoriasis and abolished AMP-IBP5-mediated improvement in psoriasis, suggesting that LRP1 is crucial in the pathogenesis of psoriasis and that LRP1 pathway is necessary for AMP-

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IBP5-induced improvement in psoriasis. Collectively, we provide evidence that AMP-IBP5 might be a novel potential therapeutic target for the treatment of psoriasis.

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Author contributions

Conceptualization: SY, GP and FN; Data curation: SY and GP; Funding acquisition: GP and FN; Methodology: SY, GP and FN; Supervision: GP and FN; Visualization: SY and GP; Writing, original draft preparation: SY and GP; Writing, review and editing: SY, GP and FN. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors have no conflicts of interest to report.

Original Articles

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Dictyostelium Differentiation-inducing Factor Derivatives Reduce the Glycosylation of PD-L1 in MDA-MB-231 Human Breast Cancer Cells

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Objectives: Triple-negative breast cancer (TNBC) is a metastatic and intractable cancer with limited treatment options. Refractory cancer cells often express the immune checkpoint molecules programmed death-ligand 1 (PD-L1) and PD-L2, which inhibit the anticancer effects of T cells. Differentiation-inducing factors, originally found in *Dictyostelium discoideum*, and their derivatives possess strong antiproliferative activity, at least in part by reducing cyclin D1 expression in various cancer cells, but their effects on PD-L1/PD-L2 have not been examined. In this study, we investigate the effects of six DIF compounds (DIFs) on the expression of PD-L1/PD-L2 and cyclin D1/D3 in MDA-MB-231 cells, a model TNBC cell line.

Methods: MDA-MB-231 cells were incubated for 5 or 15 h with or without DIFs, and the mRNA expression of cyclin D1, PD-L1, and PD-L2 were assessed by quantitative polymerase chain reaction (qPCR). Whereas, MDA-MD-231 cells were incubated for 12 or 24 h with or without DIFs, and the protein expression of cyclins D1 and D3, PD-L1, and PD-L2 were assessed by Western blotting.

Results: As expected, some DIFs strongly reduced cyclin D1/D3 protein expression in MDA-MB-231 cells. Contrary to our expectation, DIFs had little effect on PD-L1 mRNA expression or increased it transiently. However, some DIFs partially reduced glycosylated PD-L1 and increased non-glycosylated PD-L1 in MDA-MB-231 cells. The level of PD-L2 was very low in these cells.

Conclusion: Since PD-L1 glycosylation plays an important role in preventing T cells from attacking cancer cells, such DIFs may promote T cell attack on cancer cells *in vivo*.

Key words: *Dictyostelium*, differentiation-inducing factor 1 (DIF-1), triple-negative breast cancer, programmed cell death 1 (PD-1), programmed death-ligand 1 (PD-L1)

Introduction

The elucidation of mechanisms underlying immunosuppression by programmed cell death protein 1 (PD-1)[1)] and its ligand, programmed death-ligand 1 (PD-L1)[2)], has led to great progress in the field of cancer immunotherapy. PD-L1 is an immune checkpoint inhibitor that promotes immunosuppression by binding to PD-1 on immune cells[3-7)]. Normal (non-transformed) cells in the body are not attacked by immune cells, whereas cancer (transformed) cells are recognized as "non-self" and are attacked by T cells[8, 9)]. However, cancer cells expressing PD-L1 can evade immune destruction by binding to PD-1 on the surface of T cells[6, 10-12)]. After the discovery of PD-L1, the PD-L2

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ligand, which has the same action as PD-L1, was also identified[7, 13]. Nivolumab/Opdivo®, an anti-PD-1 antibody approved for the treatment of various types of cancer, acts by blocking the interaction of PD-1 with PD-L1 and PD-L2, thereby releasing immunosuppression and promoting the tumor-killing effect of T cells[4, 7, 14]. Accordingly, the application of immune checkpoint inhibitors such as anti-PD-1 and anti-PD-L1/PD-L2 and inhibitors for PD-L1/PD-L2 expression is rapidly becoming a promising cancer immunotherapy approach[4-7, 15].

Breast cancer is the most common cancer among women, accounting for about 25% of all new female cancers each year[16, 17]. Triple-negative breast cancer (TNBC) is a subtype of breast cancer that does not express the estrogen receptor, progesterone receptor, or human epidermal receptor 2, with clinical features that include being highly proliferative, metastatic, heterogenous, and refractory. Due to the lack of targetable receptors, targeted hormone therapies for TNBC are not an option[18-21]. Therefore, innovative breast cancer treatments, including novel anticancer and antimetastatic drugs, are needed. PD-L1 is expressed in 20% of TNBCs, suggesting that it may serve as a therapeutic target in this disease[22-24].

Differentiation-inducing factor 1 (DIF-1, 1-(3,5-dichloro-2,6-dihydroxy-4-methoxyphenyl) hexan-1-one) and DIF-3 (1-(3-chloro-2,6-dihydroxy-4-methoxyphenyl) hexan-1-one) are chlorinated alkylphenones (Figure 1) that were originally isolated as inducers of stalk cell differentiation from the cellular slime mold *Dictyostelium discoideum*[25-27]. Subsequently, DIFs and several of their derivatives were found to have antiproliferative and antimetastatic activities in mammalian tumor cells both *in vitro* and *in vivo*[28-42]. Recently, we found that several DIF derivatives (of the 43 assessed) strongly suppressed the proliferation and/or serum-induced migration of MDA-MB-231 cells, a model TNBC cell line[43]; thus, DIFs have therapeutic potential in the treatment of TNBC. Because MDA-MB-231 cells express PD-L1 and PD-L2[24, 44], they can be used as a model for the development of therapeutic methods and drugs targeting PD-L1/PD-L2.

In this study, we assessed the effects of six representative DIF compounds (Figure 1) on the expression of PD-L1 and PD-L2 in MDA-MB-231 cells. The results showed that although DIF compounds had little effect on PD-L1/PD-L2 protein expression or slightly decreased it, some of the DIF compounds significantly reduced glycosylated PD-L1 and increased non-glycosylated PD-L1, which may reduce PD-L1 activity. Thus, such compounds might inhibit PD-1/PD-L1 signaling, thereby facilitating activation of T cells that then attack cancer cells.

Materials and Methods

1. Cells and reagents

Human MDA-MB-231 cells were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA) and grown and maintained at 37°C with 5% CO_2 and 95% air in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS), 4.5 g/L glucose, and antibiotics (75 μg/mL penicillin and 50 μg/mL streptomycin). DIF compounds were synthesized as previously described[34] and stored as 10 mM stock solutions in dimethyl sulfoxide (DMSO) at -20°C.

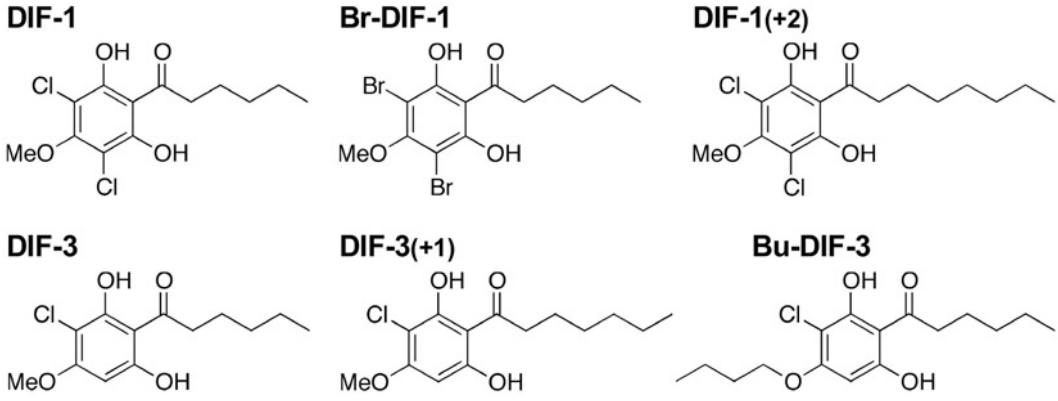

Figure 1 Chemical structure of six differentiation-inducing factor (DIF) compounds

2. Cell proliferation assay

MDA-MB-231 cells were incubated in 12-well plates (Corning, New York, NY, USA) with each well containing 1 ml of DMEM-FBS (2×10^4 cells/1 mL/well) until cells attached to the bottom of the wells. After removal of the media, cells were incubated for 3 days with 1 mL DMEM-FBS containing 0.2% (v/v) DMSO or 10 or 20 μM DIF compounds. Then, the cells were observed by phase-contrast microscopy and re-incubated with 1 mL of fresh DMEM-FBS containing 5% (v/v) of the cell number indicator Alamar blue (Wako Pure Chemical Industries, Osaka, Japan) until color of the media had changed. Relative cell number was determined by measuring absorbance at 570 nm (reference at 595 nm), as described previously[31, 34].

3. Quantitative polymerase chain reaction (PCR)

MDA-MB-231 cells were grown in 10 cm tissue culture dishes (Corning) to 60-80% confluence in DMEM-FBS. Then the media were removed, and cells were incubated for 5 and 15 h with 10 mL DMEM-FBS containing 0.2% (v/v) DMSO or 10 and 20 μM DIF compounds. After washing the cells with 10 mL phosphate-buffered saline (PBS), cells were lysed in 1 mL Isogen (Nippon Gene Co., Ltd., Tokyo, Japan). Total RNAs were prepared from the lysates, followed by reverse transcription of 1 μg RNA into cDNA by using the High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. We performed quantitative PCR (qPCR) to assess the relative mRNA levels of cyclin D1, PD-L1, and PD-L2 by using the TaqMan Gene Expression Master Mix (Applied Biosystems, Foster City, CA, USA) and LightCycler Nano Instrument (Roche, Basel, Switzerland), with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) serving as the internal control. The following primers were used: cyclin D1, Hs00765553_m1; PD-L1, Hs00204257_m1; PD-L2, Hs00228839_m1; and GAPDH, Hs99999905_m1 (Thermo Fisher Scientific).

4. Western blot analysis

MDA-MB-231 cells were incubated in 12-well plates (Corning) with each well containing 1 ml of DMEM-FBS ($5\text{-}10 \times 10^4$ cells/mL/well) until cells attached to the bottom of the wells. After removal of the media, cells were incubated for 12 and 24 h with 1 mL DMEM-FBS containing 0.2% (v/v) DMSO or 10 or 20 μM DIF compounds. Then cells were washed with 1 mL PBS, harvested by adding 0.1-0.2 ml of SDS-sample buffer solution (in proportion to cell density: relative cell number), crushed and heated by sonication, and used for sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Western blot analysis was performed as previously described[35]. Briefly, proteins were resolved by SDS-PAGE and electrotransferred to membranes. After blocking with 0.3% non-fat dry-milk powder in a Tris-buffered saline (10 mM Tris-HCl, pH 7.5, 137 mM NaCl, 0.1% Tween 20; designated TBS-T hereafter) for 1 h at room temperature, the membranes were incubated for 1 h at room temperature with primary antibodies against cyclin D1, cyclin D3, PD-L1, PD-L2, or GAPDH in TBS-T. After washing with TBS-T, membranes were incubated for 1 h at room temperature with anti-mouse alkaline phosphatase or anti-rabbit IgG secondary antibody in TBS-T. Visualization of the protein bands was performed in an alkaline buffer (100 mM Tris-HCl, pH 9.5, 100 mM NaCl, 5 mM $MgCl_2$) containing 5-bromo-4-chloro-3-indolyl-phosphate (62.5 μg/ml) and nitro blue tetrazolium (125 μg/ml); the labeled protein bands were quantified with Adobe Photoshop Element 2020 (Adobe, San Jose, CA, USA) and ImageJ software (version 1.53a).

5. Statistical analyses

Statistical analyses were performed using the Welch's t-test (two-tailed) with $p<0.05$ considered statistically significant.

Results

1. Selection of six DIF compounds for evaluation

We first compared and evaluated the antitumor activity of six DIF compounds in MDA-MB-231 cells and LM8 murine osteosarcoma cells for comparison (Table 1). Because the antiproliferative and antimigratory activities of the natural compounds, DIF-1 and DIF-3, are comparatively weak in MDA-MB-231 cells and LM8 cells, we selected three compounds, one derivative of DIF-1 and two derivatives of DIF-3. Of the three compounds, Br-DIF-1 (1-(3,5-dibromo-2,6-dihydroxy-4-methoxyphenyl)hexan-1-one) is charac-

Table 1 Antiproliferative and antimigratory activities of DIF compounds

	IC_{50} (μM) vs. Cell growth		IC_{50} (μM) vs. Cell migration	
Compound	MDA-MB-231[43]	LM8[36]	MDA-MB-231[43]	LM8[36]
DIF-1	> 20	18.2	> 10	8.5
Br-DIF-1	> 20	18.5	3.8	5.5
DIF-1(+2)	n.d.	n.d.	> 10	n.d.
DIF-3	> 20	15.5	> 10	10.2
DIF-3(+1)	12.2	7.8	> 10	5.1
Bu-DIF-3	6.0	2.0	3.9	4.2

Footnote: n.d., not determined.

teristic in the following points. The antiproliferative activity of Br-DIF-1 is comparatively weak in both cell lines but it strongly suppresses the serum-induced migration of MDA-MB-231 cells[43] and lysophosphatidic acid-induced migration of LM8 cells[36] (Table 1); therefore, Br-DIF-1 may be a good lead compound for the development of antimetastatic agents. Whereas, DIF-3(+1) (1-(3-chloro-2,6-dihydroxy-4-methoxyphenyl)heptan-1-one) and Bu-DIF-3 (1-(3-chloro-2,6-dihydroxy-4-butoxyphenyl) hexan-1-one) are characteristic in the following points. The antiproliferative and antimigratory activities of DIF-3(+1) and Bu-DIF-3 are comparatively strong in both cell lines (Table 1); therefore, DIF-3(+1) and Bu-DIF-3 may be good lead compounds for the development of antiproliferative and antimetastatic agents. On the other hand, the antiproliferative and antimigratory activities of DIF-1(+2) (1-(3,5-dichloro-2,6-dihydroxy-4-methoxyphenyl)octan-1-one) are weak in both cell lines (Table 1), but as this derivative has strong antimalarial activity[45], we used it for subsequent comparative analyses. In this study, we reconfirmed the effects of these DIF compounds on cell proliferation and morphology in MDA-MB-231 cells (Figure 2), where we used DIF-1, Br-DIF-1, DIF-1(+2), DIF-3, and DIF-3(+1) at 20 μM and Bu-DIF-3 at 10 μM since Bu-DIF-3 at more than 10 μM is highly toxic to the cell. The concentrations of these compounds are omitted hereafter unless otherwise needed.

2. Effects of DIFs on cyclin D1 expression in MDA-MB-231 cells

DIF-1 and DIF-3 suppress cell proliferation, at least in part, by reducing cyclin D1 expression in many cancer cell lines[33, 35, 42, 46-48]. To confirm the general actions of DIFs, we first evaluated the effects of the six DIF compounds on cyclin D1 mRNA expression in MDA-MB-231 cells (Figure 3A). Cyclin D1 mRNA expression was not significantly suppressed after 5 and 15 h of incubation with DIF-1 and its derivatives except for Br-DIF-1, which slightly suppressed expression at 5 h. In contrast, DIF-3, DIF-3(+1), and Bu-DIF-3 significantly suppressed cyclin D1 mRNA expression after 5 h; after 15 h of incubation, only DIF-3(+1) significantly suppressed expression.

Next, we examined the effects of DIFs on the protein expression of D-type cyclins D1 and D3 in MDA-MB-231 cells; note that the cells were alive and healthy up to 24 h of incubation with the DIFs (Figure 4) until the cells were collected for Western blot analysis. Expression of cyclins D1 and D3 was not significantly changed after 12 and 24 h of incubation with DIF-1 and its derivatives (Figure 5A); however, DIF-3, DIF-3(+1), and Bu-DIF-3 significantly suppressed expression of both cyclins D1 and D3 protein after 12 and 24 h of incubation except for cyclin D1 with DIF-3 at 24 h (Figure 5B). These results showed that at the indicated concentrations, DIF-1 compounds had little effect on cyclins D1 and D3 protein expression but DIF-3 compounds reduced their expression in MDA-MB-231 cells.

3. Effects of DIFs on the expression of PD-L1 and PD-L2 in MDA-MB-231 cells

To verify whether DIFs might be useful for cancer immunotherapy, we assessed the effects of the six DIFs on the expression of PD-L1 and PD-L2 mRNA in MDA-MB-231 cells (Figure 3B, C). Contrary to our expectation, Br-DIF-1, DIF-3, DIF-3(+1), and Bu-DIF-3 transiently increased PD-L1 mRNA

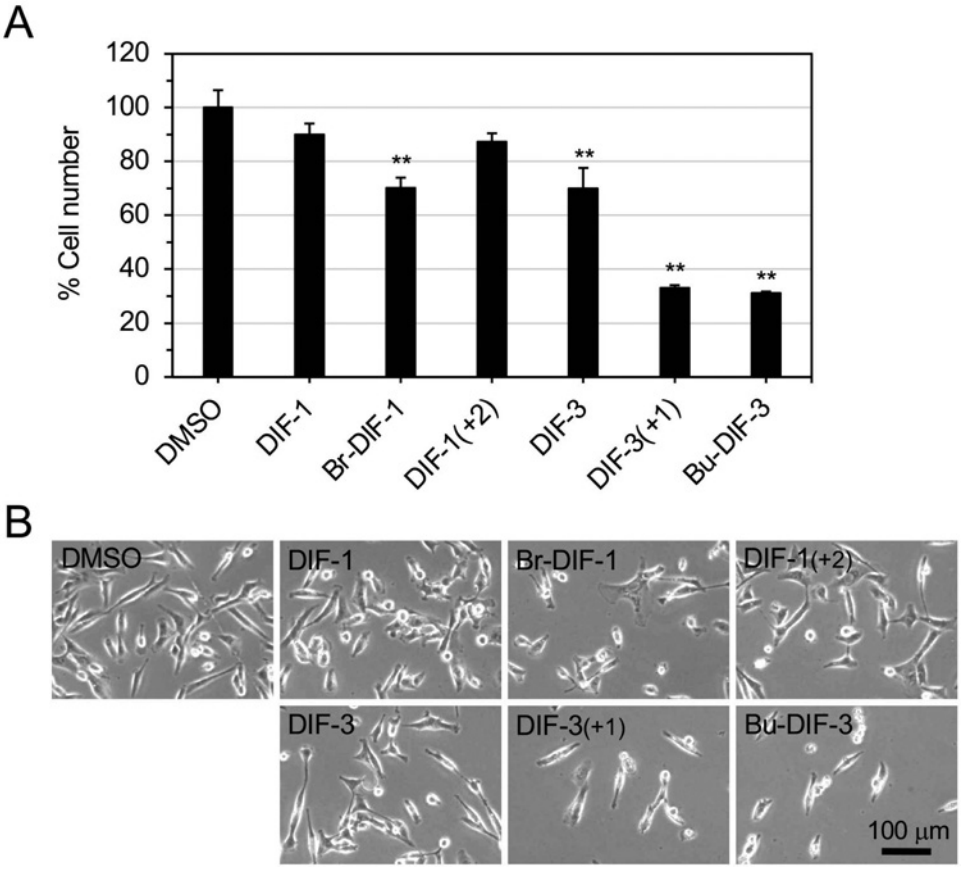

Figure 2 Effects of DIF compounds on cell growth and morphology in MDA-MB-231 cells. Cells were incubated for 3 days with 0.2% DMSO or 20 μM DIF-1 or its derivatives, or with 20 μM DIF-3 or DIF-3(+1) or 10 μM Bu-DIF-3, and relative cell number was determined; data are the mean ± standard deviation of a single experiment performed in triplicate (**A**). $^{**}p < 0.01$ *vs.* DMSO control. Representative photos of the cells at Day 3 are shown in (**B**).

expression after 5 h of incubation but did not significantly affect expression at 15 h (Figure 3B), whereas DIF-1 and DIF-1(+2) did not significantly affect PD-L1 mRNA expression after 5 or 15 h of incubation. PD-L2 mRNA expression was not significantly affected after 5 and 15 h of incubation with DIF-1, its derivatives, and DIF-3, but it was slightly increased after 5 h of incubation with DIF-3(+1) or Bu-DIF-3 (Figure 3C).

Next, we evaluated the effects of DIFs on the expression of PD-L1 (Figure 5C, D) and PD-L2 proteins (Figure 5E, F) in MDA-MB-231 cells. Because PD-L1 has four asparagine residues modified with sugar chains[49, 50], Western blotting detects multiple bands with different molecular weights. We quantified the amounts of total PD-L1 (PD-L1^{total}), unmodified PD-L1 (PD-L1^{low}, ~33 kDa), and glycosylated PD-L1 (PD-L1^{hi}, max ~50 kDa). The expression of total PD-L1 protein was not significantly affected after 12 and 24 h of incubation with DIF-1, DIF-1(+2), or DIF-3, whereas Br-DIF-1, DIF-3(+1), and Bu-DIF-3 significantly reduced PD-L1^{total} by an average of 5-10% by 24 h (Figure 5C, D). Interestingly, however, all six DIFs tended to increase PD-L1^{low} and reduce PD-L1^{hi} at both timepoints. In particular, by 24 h Br-DIF-1, DIF-3(+1), and Bu-DIF-3 significantly increased PD-L1^{low} by an average of 15-20% and significantly reduced PD-L1^{hi} by an average of 15-20% (Figure 5C, D), suggesting that these DIF derivatives might increase PD-L1^{low}, possibly by reducing either PD-L1^{hi} or PD-L1^{total}, or both. Because the protein expression of PD-L2 was low overall, only the total amount of PD-L2 protein was quantified (Figure 5E, F). Only Br-DIF-1 at 24 h and DIF-3 and DIF-3(+1) at 12 h significantly reduced PD-L2 expression.

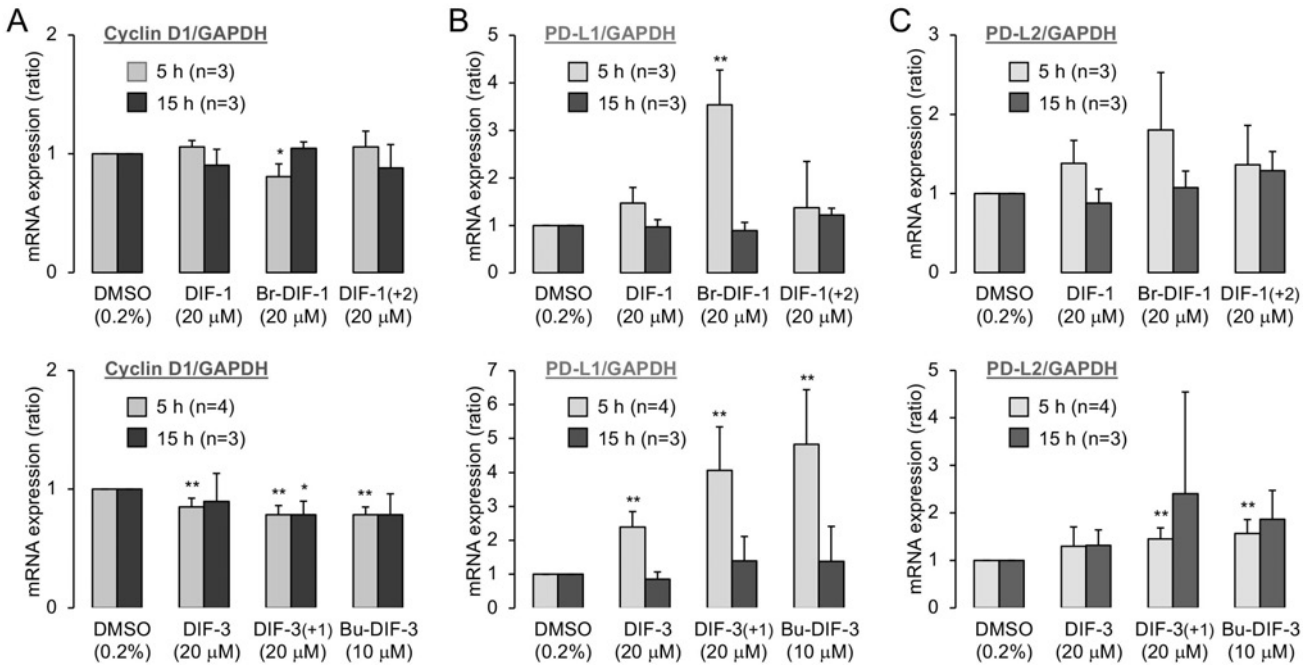

Figure 3 Effects of DIFs on the mRNA expression of cyclin D1 (**A**), PD-L1 (**B**), and PD-L2 (**C**) in MDA-MB-231 cells, as assessed by qPCR. Cells were incubated for 5 or 15 h in the presence of DMSO (control) or the indicated DIFs. The mean ± standard deviation of 3 or 4 independent experiments relative to control are shown. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* DMSO control. GAPDH is glyceraldehyde-3-phosphate dehydrogenase.

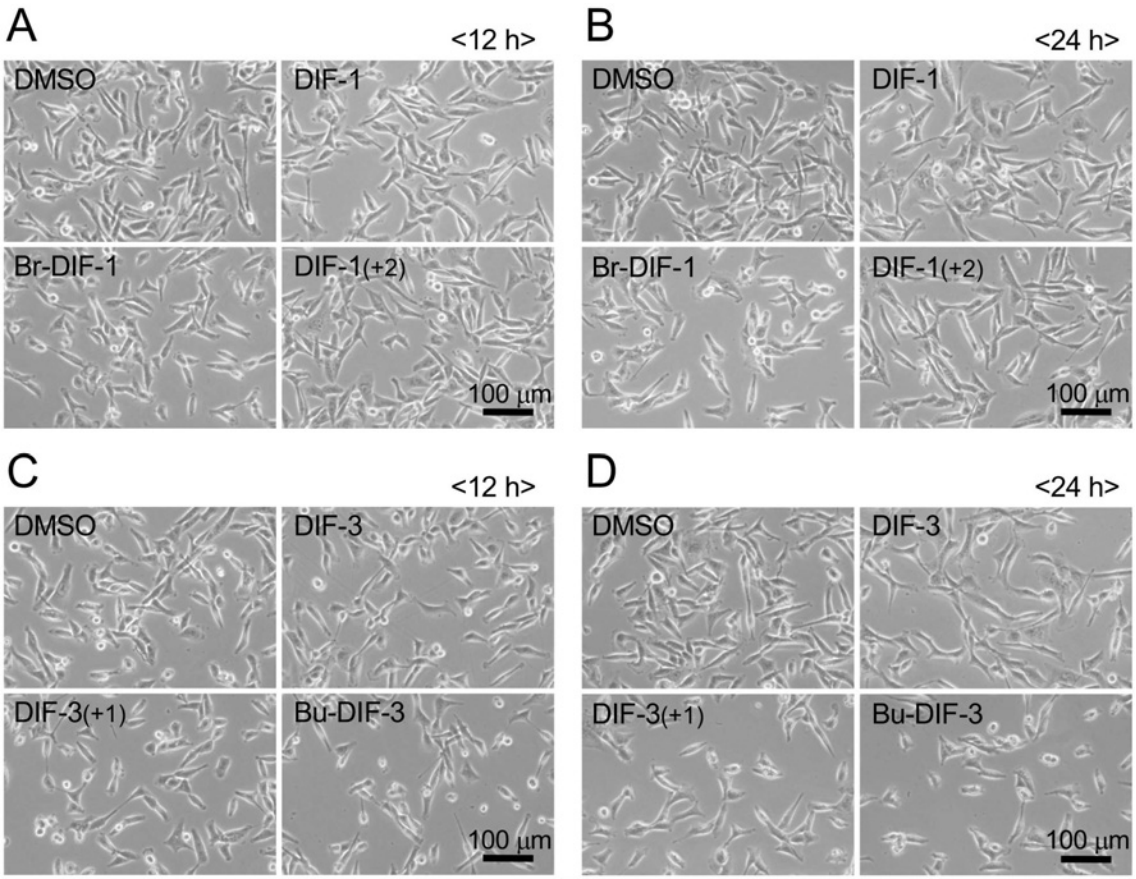

Figure 4 Representative phase-contrast images of MDA-MB-231 cells incubated with DIFs or DMSO control. Cells were incubated for 12 h (**A, C**) or 24 h (**B, D**) with 0.2% DMSO or 20 μM DIF-1 or its derivatives (**A, B**), or with 20 μM DIF-3 or DIF-3(+1) or 10 μM Bu-DIF-3 (**C, D**). These cells were used for Western blotting.

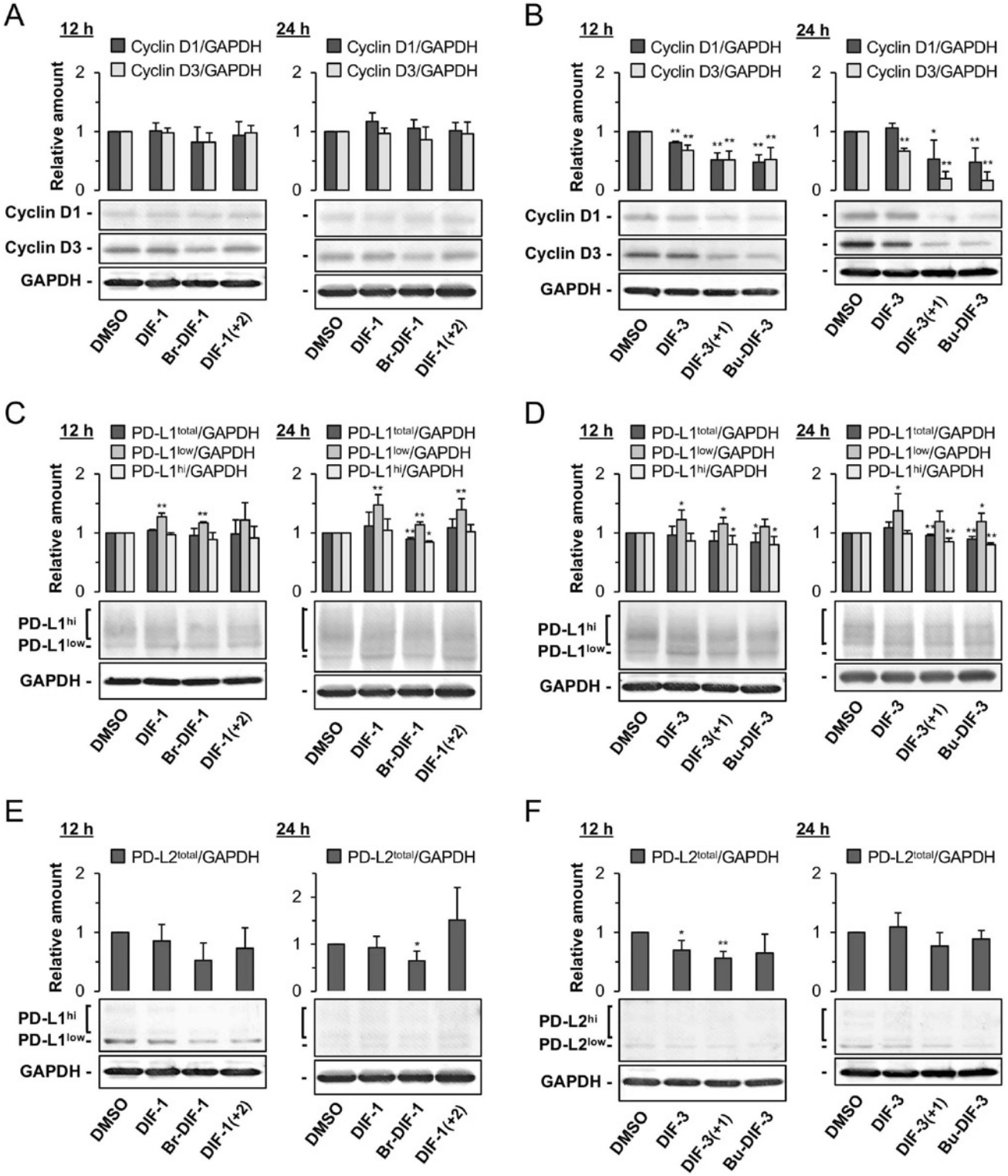

Figure 5 Effects of DIFs on the protein expression of cyclins D1 and D3 (**A, B**), PD-L1 (**C, D**), and PD-L2 (**E, F**) in MDA-MB-231 cells, as assessed by Western blotting. Cells were incubated for 12 h or 24 h with 0.2% DMSO (control) or 20 μM DIF-1 or its derivatives (**A, C, E**), or with 20 μM DIF-3 or DIF-3(+1) or 10 μM Bu-DIF-3 (**B, D, F**). The amounts of cyclins D1 and D3 (**A, B**), the amounts of total PD-L1 (PD-L1^{total}), non-glycosylated PD-L1 (PD-L1^{low}), and glycosylated PD-L1 (PD-L1^{hi}) (**C, D**), and the amounts of total PD-L2 (**E, F**) were normalized with GAPDH and shown relative to those with DMSO. The mean ± standard deviation of three independent experiments relative to control are shown together with representative images of the blots. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs*. DMSO control.

Discussion

1. Antiproliferative and antimigratory effects of DIF on MDA-MB-231 cells

DIF-1, DIF-3, and their derivatives have antiproliferative and/or antimigratory activities in a variety of tumor cells *in vitro* and *in vivo*[28-42], and are expected to be lead compounds for the development of anticancer agents. We previously showed that several DIF derivatives, such as DIF-3(+1) and Bu-DIF-3, strongly suppressed both the proliferation and serum-induced migration of MDA-MB-231[43] (Table 1), while another group showed that 30 μM DIF-1 significantly suppressed the proliferation of MCF-7 human breast cancer cells *in vitro*, at least in part via the reduction of cyclin D1 expression[51]. More recently, the same group has shown that 30 μM DIF-1 inhibited the proliferation and migration of MDA-MB-231 cells *in vitro*, and 150 mg/kg DIF-1 (administered every 12 h for 14 days to mice) inhibited the growth and metastasis of TNBC cells *in vivo*[48]. Herein, we confirmed that DIF-3(+1) and Bu-DIF-3, the most promising DIF derivatives as anticancer agents evaluated in this study, may suppress cell proliferation in MDA-MB-231 cells, at least in part by reducing the expression of cyclins D1 and D3 (Figure 3A, 5B).

2. Suppression of PD-L1 glycosylation by DIF

As described in the Introduction section, because MDA-MB-231 cells express the immune checkpoint molecules PD-L1 and PD-L2[24, 44], these cells can be used for screening candidate agents targeting PD-L1/PD-L2. Here, we evaluated the effects of six DIFs (Figure 1) on the expression of PD-L1 and PD-L2 in MDA-MB-231cells (Figure 3B, C, 5C-F). Initially, we expected the DIFs to suppress expression of PD-L1 and PD-L2; contrary to our expectations, Br-DIF-1, DIF-3, DIF-3 (+1), and Bu-DIF-3 transiently increased the mRNA expression of PD-L1 at 5 h (Figure 3B), whereas the total protein expression of PD-L1 was not significantly increased after 12 and 24 h of incubation with the DIFs (Figure 5C, D). The reason for the transient increase in PD-L1 mRNA expression is unknown, but, for example, DIFs might induce a transient increase in PD-L1 mRNA expression as a secondary effect of arresting cell cycle. In any case, since protein expression is generally regulated by the balance between mRNA translation and protein degradation, any PD-L1 protein synthesized at 5 h may have been degraded to some extent by 12 h during incubation with DIFs.

Interestingly, Br-DIF-1, DIF-3(+1), and Bu-DIF-3 reduced PD-L1^{total} at 24 h (Figure 5C, D) and tended to increase the amount of PD-L1^{low}, possibly by reducing PD-L1^{hi} (glycosylated PD-L1) (Figure 5C, D). Glycosylation of PD-L1 is essential for the PD-L1/PD-1 interaction and immunosuppression in TNBC[52]. Glycosylated PD-L1 becomes resistant to degradation by the proteasome and stabilizes[49]. Therefore, inhibition of PD-L1 glycosylation by DIFs might lead to inhibition of PD-L1/PD-1 signaling, thereby reducing immunosuppression of T cells and facilitating their attack on cancer cells (Figure 6).

The expression of PD-L2 protein was decreased by treatment with Br-DIF-1 at 24 h and DIF-3 and DIF-3(+1) at 12 h (Figure 5E, F). However, as the expression level of PD-L2 is considerably low in MDA-MB-231 cells (Figure 5E, F), it is unknown whether these levels of PD-L2 are involved in immunosuppression of T cells.

Herein, we assessed the effects of DIF-1(+2) on the expression of cyclins D1 and D3 and PD-L1/PD-L2 in MDA-MB-231 cells, as DIF-1(+2) has antimalarial activity[45]. The only significant biological activity of DIF-1(+2) in these cells was a significant increase in PD-L1^{low} (Figure 5C).

Conclusions

In this study, we assessed the effects of six DIF compounds on the expression of PD-L1 and PD-L2 in MDA-MB-231 cells and found that Br-DIF-1, DIF-3(+1), and Bu-DIF-3 reduced PD-L1 glycosylation. Our results suggest that such compounds might inhibit PD-L1/PD-1 signaling and thereby reduce immunosuppression of T cells, thus facilitating their attack of cancer cells (Figure 6), although it is currently unknown whether such a DIF-induced reduction in glycosylation actually affects T cell activity. Accordingly, DIFs may be good lead compounds for the development not only of antiproliferative and antimigratory (antimetastatic) drugs but also of immunotherapy drugs against TNBC and possibly some other metastatic cancers. It may be worth investigating the inhibitory effects of other DIF derivatives (~50 DIF

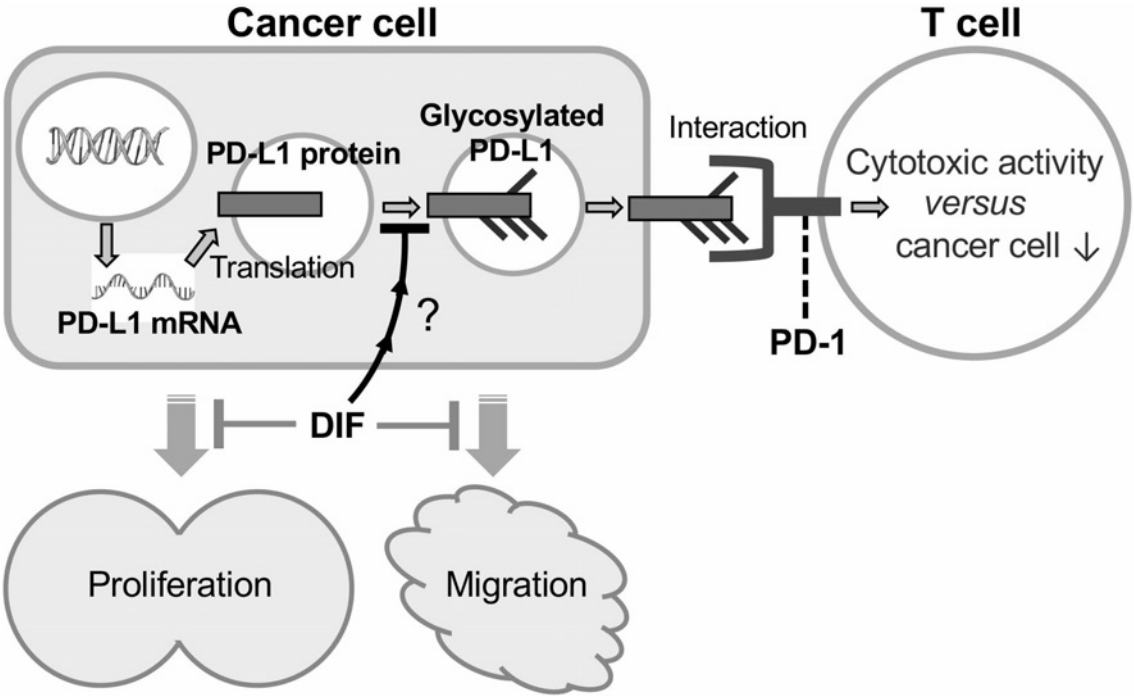

Figure 6 Schema of the processing pathway of PD-L1 and the action of DIFs. After translation from PD-L1 mRNA, PD-L1 protein is glycosylated at four asparagine residues (N35, N192, N200, and N219)[50]. N-glycosylated PD-L1 binds to its receptor PD-1 on T cells, which suppresses the cytotoxic activity of T cells, thereby allowing cancer cells to escape attack from T cells. DIF might be able to weaken PD-L1/PD-1 interaction by inhibiting glycosylation of PD-L1 and thus facilitating restoration of T cell immunity to some extent. In addition, DIF can suppress cell proliferation and migration (metastasis) of some cancer cells including TNBC[36), 38), 41), 43), 48), 51)]; *e.g.* Bu-DIF-3 strongly suppresses cell proliferation and migration of MDA-MB-231 and LM8 cells (Table 1)[36), 43)].

derivatives in total)[34, 40, 43)] on PD-L1 and PD-L2 protein expression in MDA-MB-231 cells as well as in other cancer cells.

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Author contributions

Conceptualization, YK; methodology, HK and YK; validation, AH and YK; data analysis and investigation, AH, HI, KT, YM and YK; synthesis of compounds, HK; original draft preparation, KT and YK; review and editing, AH, HI, YM and HK. All authors have read and approved the final manuscript.

Conflicts of interest statement

The authors declare no conflict of interest.

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Original Articles

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Lateral Femoral Cutaneous Nerve Block for Postoperative Pain Control After Total Hip Arthroplasty Using the Direct Anterior Approach: A Single-blinded Randomized Control Trial

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Background: Total hip arthroplasty (THA) employing the direct anterior approach (DAA) is increasingly performed as a less invasive procedure with faster recovery than other approaches. Unlike other approaches, the skin incision is made on the lateral thigh, distal to the inguinal ligament. However, the effectiveness of ultrasound-guided lateral femoral cutaneous nerve (LFCN) block for postoperative analgesia after THA using DAA has not been investigated.
We hypothesized that ultrasound-guided LFCN block using DAA would reduce postoperative pain after THA.
Methods: A prospective, randomized, observer-blinded controlled trial was conducted. The 92 patients included were divided into two groups: those who received only femoral nerve block (FNB group) and those who received femoral nerve block and LFCN block with 10mL of 0.25% levobupivacaine (FNB + LFCNB group). Both groups received intravenous patient-controlled analgesia (fentanyl) postoperatively. A numerical rating scale was used to quantify pain at 3 and 48 h postoperatively.
Results: There was no significant difference in pain at rest and during movement between the FNB and FNB + LFCNB groups (at rest: Z = −1.6814, p=0.0927; during on movement: Z = −0.9677, p=0.9487). There was also no significant difference in pain severity at rest and during movement between the FNB and FNB + LFCNB groups postoperatively.
Conclusions: LFCNB did not improve postoperative pain relief in patients undergoing THA with DAA.

Key words: lateral femoral cutaneous nerve, nerve block, lateral femoral nerve, total hip arthroplasty, direct anterior approach

Introduction

Pain control after total hip arthroplasty (THA) has previously been managed with epidural anesthesia. However, introduction of early postoperative anticoagulant therapy has led to the avoidance of catheter insertion into the central nervous system. Pain relief is now provided by various methods such as periarticular injections and intravenous patient-controlled analgesia (IV-PCA) with opioids. Peripheral nerve blocks are also an option[1]. Peripheral nerve blocks have been shown to reduce pain following THA and have effects comparable to those of anesthetic delivery to the central nervous system[2].

Compared with other approaches, THA via the direct anterior approach (DAA) is known to have a faster recovery time, with earlier ambulation and shorter hospital stay[3, 4]. Consequently, it has been adopted as a less invasive option in an increasing

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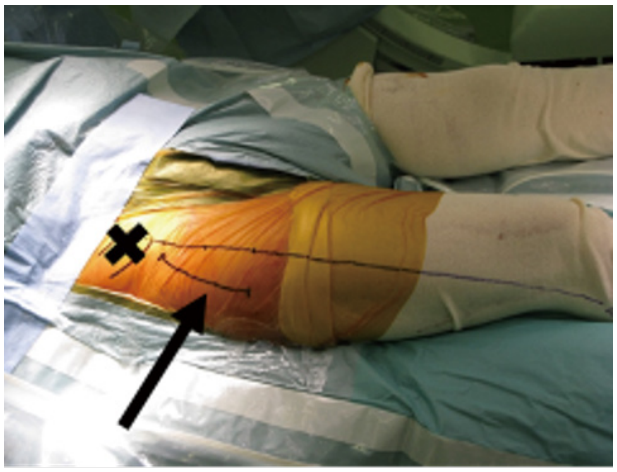

Figure 1 Total hip arthroplasty by direct anterior approach incision
Incision line is indicated by the black arrow.
Anterior superior iliac spine is indicated by a black X.

number of cases over the past decade[5,6].

In the posterior and lateral approaches, the incision is made on the back of the hip. With the DAA, the incision site is located on the lateral aspect of the thigh[5]. Figure 1 shows the skin incision site in a patient who underwent THA using DAA.

Pain sensation on the outer thigh is supplied by the lateral femoral cutaneous nerve (LFCN). Due to the great anatomical variability of the LCFN, the success rate for conventional LFCN blocks was historically low[7]; however, it has dramatically increased when used with ultrasound guidance[8].

Currently, LFCN blocks are commonly employed for postoperative analgesia. LFCN blocks have been found to decrease postoperative analgesic use in surgeries for femoral neck fractures wherein the skin incision is on the lateral thigh, similar to THA with DAA[9]. Although the efficacy of LFCN blocks for pain management after THA has been investigated several times[10,11], THA in these studies was performed with either the posterior or unspecified approaches; none of them used DAA.

In this study, we hypothesized that LFCN blocks for THA using DAA reduce postoperative pain. We compared the numerical rating scale (NRS) scores 3 h postoperatively between groups that did and did not receive an LFCN block.

Materials and Methods

Ethics approval and consent to participate

This study was approved by the hospital Ethics Committee and prospectively registered with the University Hospital Medical Information Network (UMIN: UMIN000035562) at its initiation. This study was conducted in accordance with the guidelines of the Declaration of Helsinki (2013). All study participants provided written informed consent for their participation in the study.

Study design and participants

From December 10, 2018, to August 9, 2019, we conducted a prospective, observer-blinded, comparative, and randomized controlled trial using stratified randomization at the Department of Anesthesiology and Pain Clinic, Juntendo Shizuoka Hospital, Shizuoka, Japan. The exclusion criteria were as follows: (1) previous THA on the same side; (2) presence of a lesion not suitable for skin puncture around the injection site, as determined by a surgeon; (3) history of allergic reactions to local anesthetics; (4) under anesthesia for more than 6 h; (5) dementia (Hasegawa Dementia Scale-Revised score ≤ 22 points); (6) requiring postoperative mechanical ventilation; (7) prothrombin time-international normalized ratio ≥ 2.0, activated partial thromboplastin time ≥ 1.5 × the reference value, platelet count ≤ 50,000/μL, and other clear indications for the presence of a coagulation disorder; and (8) evaluated to be ineligible by the principal investigators for any other reason. Stratified randomization was performed according to age and sex, which were considered to influence postoperative pain. The participants were patients scheduled to undergo THA using DAA at our hospital.

Patient randomization

Preoperatively, patients were randomly assigned to receive a femoral nerve block (FNB group) or FNB plus LFCN block (FNB + LFCNB group). Stratified randomization was performed using a 1:1 allocation table according to sex, and age. The patients were distributed according to the allocation table by investigators who were not directly involved in their care. The analysis was performed using an intention-to-treat analysis.

Application of anesthesia

Upon entering the operating room, all patients were connected to general monitoring equipment. They received general anesthesia with propofol,

fentanyl, remifentanil, and rocuronium, and then underwent tracheal intubation.

Preoperatively, the FNB group received FNB alone, and the FNB + LFCNB group received FNB and LFCNB. Intraoperatively, anesthesia was maintained with sevoflurane, desflurane, or propofol–rocuronium–remifentanil–fentanyl. The dose of fentanyl used during surgery was at the discretion of the anesthesiologist.

Block interventions

Four experienced anesthesiologists performed the nerve blocks. For ultrasound guidance, a 6–15–MHz linear probe of SonoSite S–Nerve (FUJIFILM Sonosite, Inc., Bothell, WA, USA) or a 4.2–13.0–MHz linear probe of the LOGIQ e premium (GE Healthcare Co., Chicago, IL, USA) was used. For the injection, a 20 G × 80 mm UNIEVER nerve block needle (Unisys Corp., Tokyo, Japan) was used.

The LFCN was identified approximately 10 cm caudal to the inguinal ligament using the fat–filled flat tunnel (FFFT, the space surrounded by the sartorius, tensor fascia lata, and rectus femoris muscles, and formed by a double layer of the fascia lata between the sartorius and tensor fascia lata muscles). Figure 2 shows the LFCN within the FFFT and at the level of the injection during the LFCNB.

After identifying the LFCN in FFFT, the echo probe was moved cranially to a position from where the LFCN could be identified sonographically. The blockade needle was inserted in–plane to inject 10 mL 0.25% levobupivacaine into the area surrounding the nerve. If the upper portion of the area could not be visualized, the drug was injected at the most superior position visible on ultrasonography, approximately 2 cm caudal to the inguinal ligament.

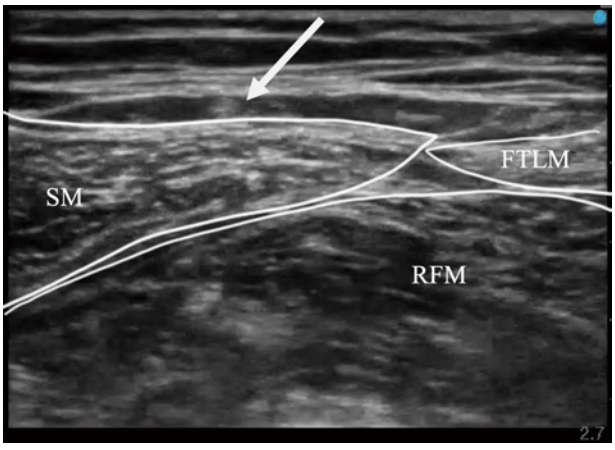

Figure 2 LFCN in FFFT
← : lateral femoral cutaneous nerve
SM : sartorius muscle, FTML : tensor fasciae latae muscle, RFM : rectus femoris muscle

Evaluation of pain

After recovering from the effects of general anesthesia, the patients were transferred to the recovery room, where postoperative assessments were conducted by a blinded observer, who was either a scrub or ward nurse. Subsequently, NRS scores at rest and on movement were measured at 3, 6, 12, 24, and 48 h postoperatively.

Postoperative analgesia

Postoperatively, all patients received fentanyl 20 μg/h with a bolus dose of 20 μg via IV–PCA for 48 h.

Outcome assessment

Postoperative pain was quantified using the NRS. The primary outcome was defined as NRS scores at rest and on movement 3 h postoperatively, and the secondary outcome as changes in NRS scores up to 48 h postoperatively.

Sample size calculation and statistical analysis

Sample size calculation was performed using R 4.0.3. The following parameters were derived from our experience and data from previous studies[12, 13]: two–tailed α=0.05, β=0.20, mean standard deviation of NRS=2.0, and δ=1.5. Using the Mann–Whitney–Wilcoxon test, the calculated sample size comprised 82 patients (41 in each group). Considering a 30% dropout rate, the final sample size was 108 patients. Intermediate analyses was not conducted. The standard deviation (SD) and interquartile range (IQR) were calculated for the average and median, respectively. For all tests and estimations, the significance level was set at 5% and a 95% confidence interval was used. In the event of missing NRS values, the multiple completion method was used to complete the data. The Mann–Whitney–Wilcoxon test was used for continuous variables, whereas the chi–square test or Fisher's exact test was used for ordinal and nominal variables. The secondary endpoint was the change in NRS at 48 h postoperatively, which was tested nonparametrically using the U test for MW and the Bonferroni method for correction of multiple comparison tests.

All analyses (except sample size calculations) were performed using the SAS software (SAS Institute Inc, NC, USA).

Results

Of the 116 patients selected, 109 were enrolled in the study. When an additional sedative, not included in the protocol was used for a patient before the measurement of the primary outcome (NRS score 3 h postoperatively), the patient was excluded. Finally, 49 patients in the FNB group and 43 in the FNB + LFCNB group were included in the analysis (Figure 3).

There were no differences in patient demographics between the two groups (Table 1).

Postoperative complication rates also did not differ between the two groups (Table 2).

There was no significant difference in NRS scores at rest and during movement 3 h postoperatively (at rest: Z = −1.6814, p=0.0927; during movement: Z = −0.9677, p=0.9487) (Figure. 4).

The change in NRS score up to 48 h postoperatively, a secondary endpoint, tended to be lower in the FNB + LFCNB group throughout the observation period, but there was no significant difference in the other measurement points between the two groups (Figure 5).

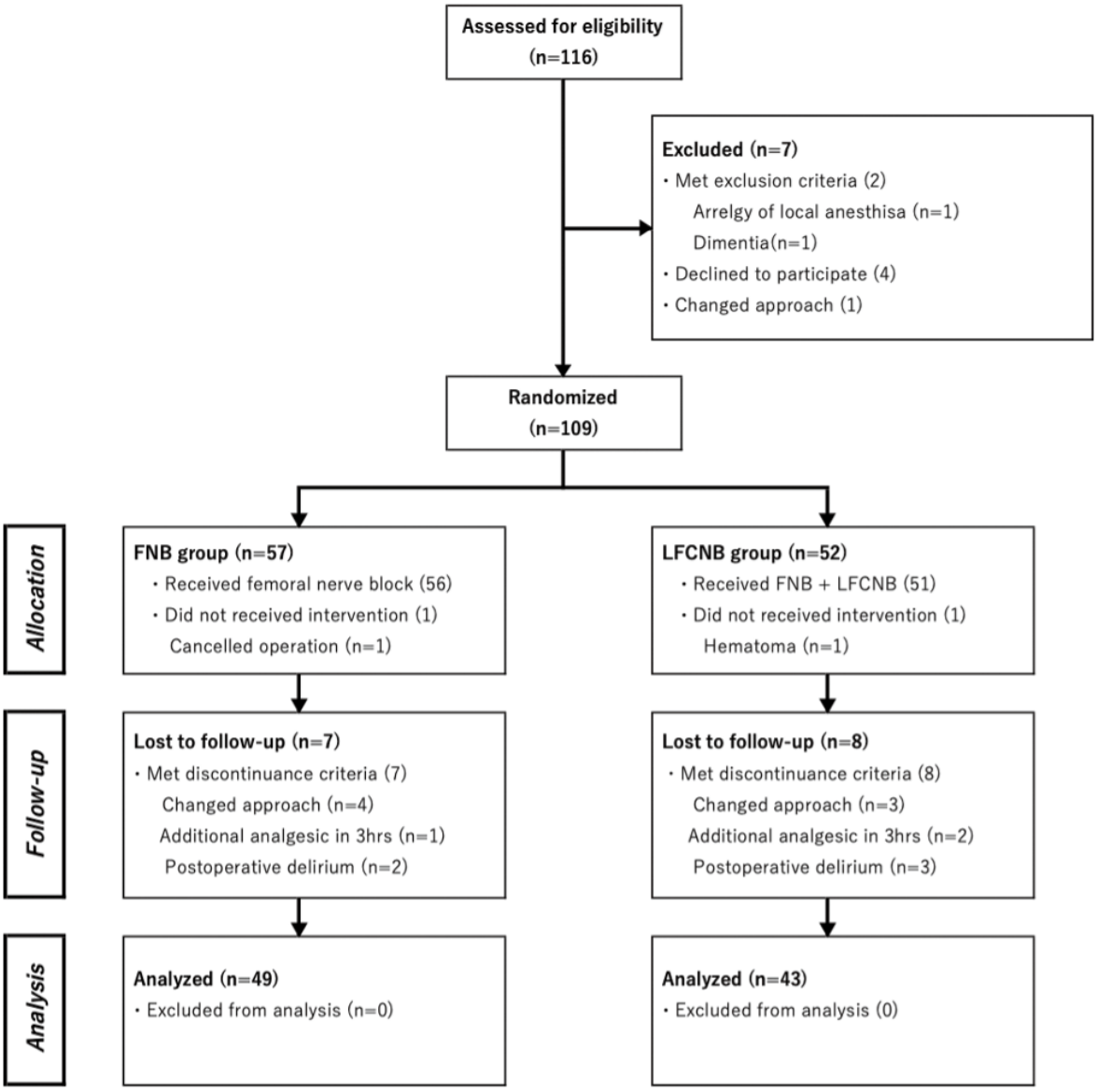

Figure 3 CONSORT diagram
FNB, femoral nerve block; LFCNB, lateral femoral cutaneous nerve block

Table 1 Basic demographics

		FNB + LFCNB group (n=43)		FNB group (n=49)		p value
Age*		67.21	(10.75)	67.33	(10.53)	0.96
Sex						
	M	12		12		
	F	31		37		
Body weight (kg)*		60.2	(10.36)	57.86	(10.58)	0.29
Body height (cm)*		157.0	(0.083)	156.9	(0.080)	0.96
ASA						
	1	7		10		
	2	31		37		
	3	5		2		
Operation time (min)*		119.04	(24.75)	115.55	(19.23)	0.12
Duration from block to start of operation (min)*		46.66	(5.86)	45.30	(6.58)	0.41

* Mean (SD)
ASA, American Society of Anesthesiology score; FNB, femoral nerve block; LFCNB, lateral femoral cutaneous nerve block

Table 2 Complications

	FNB + LFCNB group	FNB group	
PONV, n (%)	14 (33%)	15 (31%)	p=0.84 (95% CI −0.17 to 0.21)
Nerve injury, n	0	0	

CI, confidence interval; FNB, femoral nerve block; LFCNB, lateral femoral cutaneous nerve block; PONV, postoperative nausea and vomiting

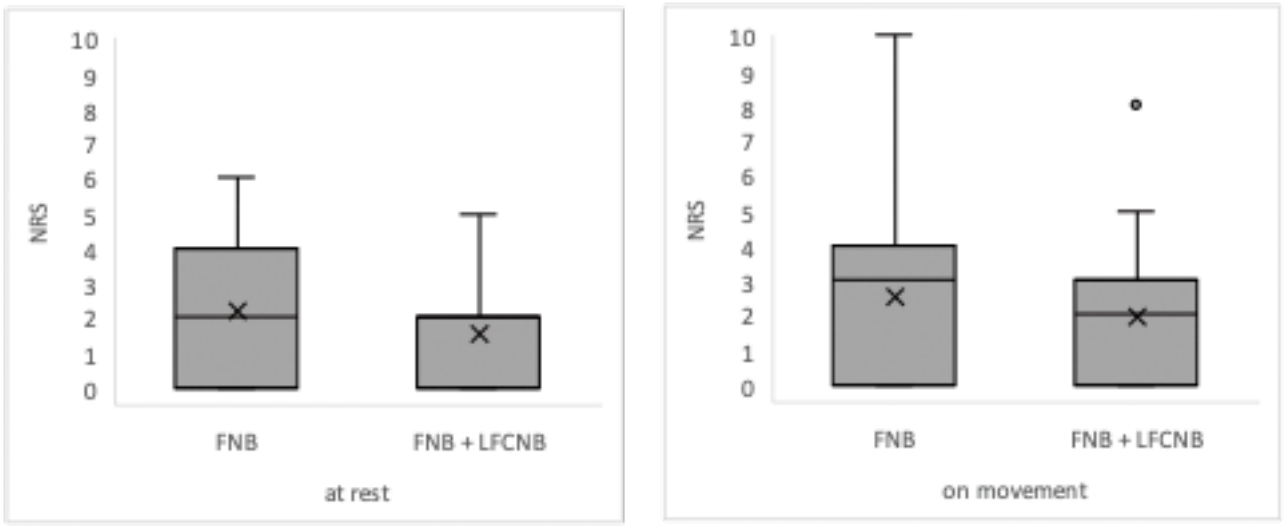

Figure 4 Pain at rest and during movement at 3 hours postoperatively
The differences were not statistically significant.
FNB, femoral nerve block; LFCNB, lateral femoral cutaneous nerve block

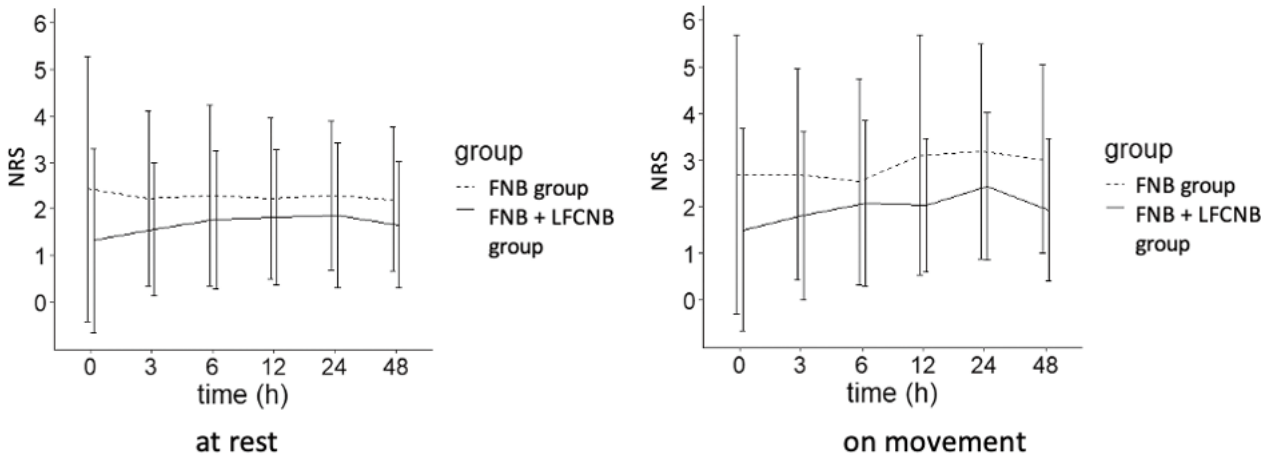

Figure 5 Pain at rest and during movement up to 48 hours postoperatively
The differences between the two groups were not statistically significant.
FNB, femoral nerve block; LFCNB, lateral femoral cutaneous nerve block

Discussion

This study found no significant difference in NRS scores at rest after THA using DAA, regardless of LFCNB use. However, no significant difference was noted between the use and non-use of LFCNB. This result is unlikely to be accidental. It is reasonable to conclude that LFCNB did not yield a significant difference in NRS scores. For the secondary outcome, that is changes in NRS scores over time, NRS scores tended to be lower in the LFCNB group throughout the observation period. However, no significant differences were observed between the groups.

One possible reason for the lack of a significant difference between the FNB and FNB + LFCNB groups could be that the wound pain associated with THA using DAA was not as severe as that associated with other approaches. THA using DAA can preserve the muscles and nerves in the thigh[14]. In fact, DAA has been shown to reduce postoperative pain compared with other approaches[4, 5, 15]. In this study, a few patients did not require additional IV-PCA. Therefore, if femoral pain was relieved with FNB, pain at the incision site on the outer thigh was controlled with fentanyl via IV-PCA and was possibly not reflected in the postoperative NRS scores. No significant differences were observed between the FNB and FNB + LFCNB groups up to 48 hours postoperatively. Another possibility is that the administration of LFCNB after general anesthesia in this study might have caused the nerve block to fail. It is possible that some patients in the FNB + LFCNB group might have failed to receive a successful block. Otherwise, the reported success rate for ultrasound-guided LFCNB was 94.7–97.5%[16, 17]. We set the dose to 10 mL in this study based on the report by Nielsen et al.[16], as it is known that a nerve block dose of ≤ 8 mL within the FFFT could reduce the success rate and extent of the drug effects[17, 18]. Thus, the possibility of nerve block failure is low. It was difficult to confirm the clinical success of LFCNB and the extent of its effects due to the concomitant general anesthesia. Nevertheless, the blocks were performed by four experienced surgeons under ultrasound guidance, and there were no cases in which the LFCN could not be identified. The low possibility of inadequate extent of the drug effects was considered. Another possible cause for the lack of significant results is the anatomical diversity of the LFCN. Studies investigating the extent of pain relief in awake patients after LFCNB have revealed greater individual differences than previously thought[16, 18, 19]. On the other hand, Nielsen et al.[16] reported that when a fascia iliaca compartment (FIC) block and an LFCNB were performed in the same patient, greater anesthetic coverage of the outer thigh was achieved with the FIC block, which was injected at a higher location than the LFCNB. This indicates that the use of the FIC block may be more desirable to ensure adequate anesthetic coverage of the outer thigh.

A limitation of this study is that the primary

outcome was defined using the subjective NRS score, which by itself is not sufficient to accurately evaluate wound pain. The NRS scores increased when there was pain in other regions. Therefore, it is necessary to consider employing scales other than the NRS. For example, it is possible that the amount of additional analgesics (i.e., fentanyl) is more suitable. Another limitation is the decision regarding exactly when to evaluate the pain. We believe that the immediate postoperative period would be strongly influenced by intraoperative opioids which were used. Therefore, we decided to set the evaluation time at 3 h postoperatively, considering that the effects of the nerve block would persist, but the blood concentration of fentanyl were also likely to be stable by this time. Casati et al. reported that a preoperative nerve block using levobupivacaine provided analgesia up to 6 h postoperatively, and we believe that this endpoint time is reasonable[20]. However, changes in the timings of the evaluation may have yielded different results.

In addition, the timing of the nerve block may also be a point of contention. Postoperative nerve blockade may have blocked acute pain and provided long-term pain relief, which again, may have shown different results.

In conclusion, LFCNB in patients undergoing THA using DAA did not demonstrate a significant difference in postoperative NRS scores when compared with IV-PCA of Fentanyl. In these cases, LFCNB did not improve postoperative pain relief.

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Author contributions

SS collected date and wrote the manuscript. TO helped edit the manuscript. SN performed statistical analysis. SS, KK, YS and MK helped performed nerve blocks. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare no competing or conflicts of interest in this work.

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Original Articles

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Serum Levels of N- and C-ERC/Mesothelin and Clinicopathological Factors in Mesothelioma Patients and Those without Mesothelioma

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Objectives: ERC/mesothelin is a glycosylphosphatidylinositol (GPI)-anchor protein expressed in mesothelioma. A precursor protein is cleaved by proteases and an N-terminal fragment (N-ERC) is extracellularly secreted. A remaining C-terminal fragment (C-ERC) is tethered on cellular membranes by the GPI-anchor, but C-ERC is also released after cleavage by proteases. We and other groups reported that serum N-/C-ERC levels are associated with stages of mesothelioma and suggested the possibility of their usefulness as diagnostic markers. However, the N-ERC level is also influenced by renal functions that are not directly associated with conditions of mesothelioma. It is not known whether other clinical factors influence serum N-/C-ERC values. Furthermore, their relationship to the amount of ERC/Mesothelin in mesothelioma is not yet validated. The objective of this study is to clarify the relationship of serum N-/C-ERC levels and the status of mesothelioma and several clinical factors.

Materials and Methods: We analyzed relations of serum N-/C-ERC levels and ages, gender and other clinical factors in 522 patients without mesothelioma and examined their relation to the amount of ERC/Mesothelin in mesothelioma tissues in 13 mesothelioma cases.

Results: Serum N-ERC levels were influenced by renal functions. On the contrary, those of C-ERC were not influenced by any clinical factors examined in this study and were significantly correlated with the amount of ERC/Mesothelin in mesothelioma.

Conclusion: Although both markers are good indicators of treatment-responses in individual patients with mesothelioma, only C-ERC reflected the amount of ERC/Mesothelin in mesothelioma among multiple patients, possibly because N-ERC was influenced by renal functions.

Key words: mesothelioma, mesothelin, expressed in renal carcinoma (ERC), N-ERC, C-ERC

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Introduction

Mesothelioma is an aggressive malignant disease arising from mesothelial cells that cover the surface of pleural, pericardial and peritoneal cavities, and is commonly associated with asbestos exposure[1]. It is intractable to conventional therapies. Even in the latest clinical trials using immune checkpoint inhibitors such as of nivolumab or pembrolizumab, the progression free survival was approximately 6 months and the overall survival was approximately 18 months[2, 3]. Unsatisfactory effects of these treatments are partly associated with the difficulty in early diagnosis of mesothelioma.

Expressed in Renal Carcinoma (ERC) was originally isolated from renal carcinoma cells of Eker rat that hereditarily develops renal carcinoma[4], and ERC is a homologue of human Mesothelin (MSLN)[5]. ERC/Mesothelin is a glycosylphosphatidylinositol (GPI)-anchor protein that is expressed on surface of normal mesothelium, epithelioid-type mesothelioma[6] or epithelioid components of biphasic mesothelioma. A 71-kDa ERC/Mesothelin-precursor protein is cleaved by proteases and a 31-kDa N-terminal fragment (N-ERC), that is identical to megakaryocyte potentiation factor (MPF)[7], is extracellularly secreted. A remaining 40-kDa C-terminal fragment (C-ERC) is tethered on cellular membranes by the GPI-anchor, but C-ERC is also released after incomplete cleavage by other proteases, and C-ERC partially remains on cellular membranes[8] (Figure 1, Supplementary Figure 1).

Asbestos/mesothelioma outpatient clinic was established in Juntendo University hospital in 2005, to screen the asbestos-exposed laborers and their family members for the early diagnosis of mesothelioma[9-10]. The patients took the regular check of chest x-ray or blood test including N-ERC and C-ERC.

We and others previously reported that both N-ERC and C-ERC serum levels are increased in mesothelioma patients and suggested that they can be useful for the early diagnosis of mesothelioma, or indicators of the effectiveness of chemotherapy or surgical treatments[11-20]. However, the relationship between their serum levels and the amount of ERC in mesothelioma tissue is not yet validated. Furthermore, Shiomi et al., reported that the serum N-ERC level is increased in patients with renal failure[21], and their findings suggested that it may be influenced by the clinical conditions that are not directly related to the status of mesothelioma. In this study, at first, we tried to clarify the relationship between the amount of ERC in mesothelioma tissue and the serum levels of N- or C-ERC. As a result, the serum levels of C-ERC were positively correlated to the amount of ERC in mesothelioma, but those of N-ERC were not. Secondly, because N-ERC is reported to be affected by the renal function, we examined whether the serum levels of N-

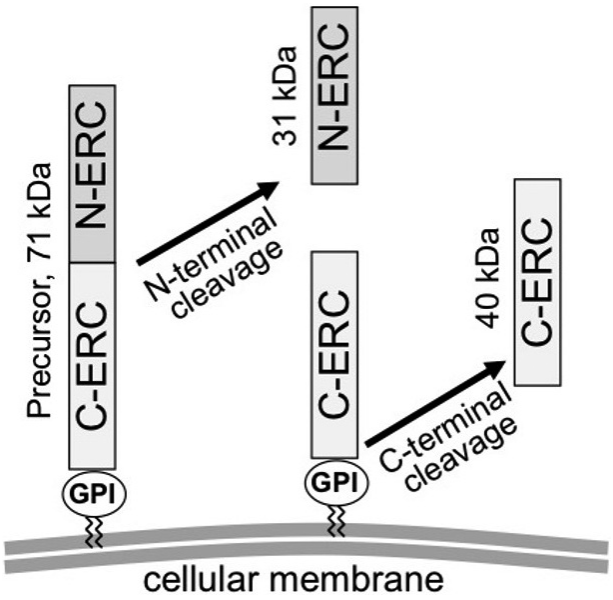
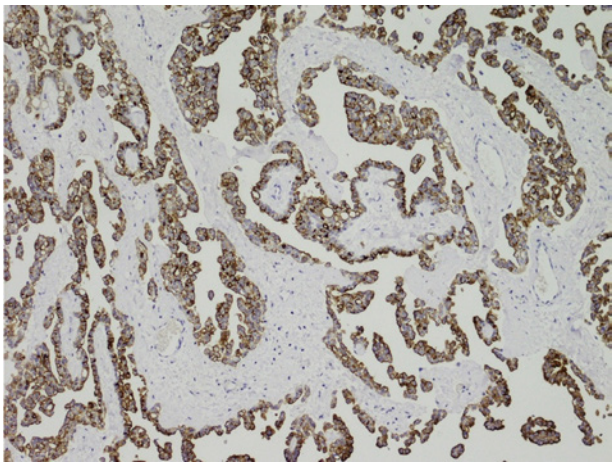


Figure 1 Structures of a 71-kD precursor ERC protein and two cleaved products, a 31-kDa N-ERC and a 40 kDa C-ERC. N-ERC and C-ERC are cleaved by proteases and released to the extracellular space. C-ERC, however, partially remains on the cellular membrane.



Supplementary Figure 1 ERC expressed in mesothelioma tissue. ERC is detected by anti-C-ERC antibody on cellular membranes of epithelioid type mesothelioma.

or C-ERC are influenced by the clinical factors that are not directly associated with the mesothelioma. As a result, the serum levels of N-ERC were influenced by the renal function, as reported previously, but those of C-ERC was not. The C-ERC levels were not influenced by any of the clinical conditions examined in this study, other than those related to mesothelioma. Thirdly, we compared the clinical factors between the patients whose N-ERC was higher than C-ERC (N-higher group) and those whose C-ERC was higher than N-ERC (C-higher group). As a result, N-higher group included more women than men ($p<0.05$), although the reason for this phenomenon is to be clarified in the future.

Our study gave us a caution that we must be careful in the interpretation of serum C- and N-ERC values as the marker of mesothelioma among different patients. Both markers are, however, still valuable to monitor the status of mesothelioma in individual patients.

Materials and Methods

1. Patients

Serum samples and biopsy or surgically resected specimens of mesothelioma were obtained from 42 mesothelioma patients and 522 outpatients who visited Asbestos/mesothelioma clinic in Juntendo University between 2005 and 2019. The patient characteristics in this study are shown in Table 1. None of 522 outpatients showed clinical evidence of mesothelioma. All procedures were performed in accordance with the Ethics Committee at Juntendo University School of Medicine (approval number: H05-0014) and with the Declaration of Helsinki. Written informed consent for participation in this study was obtained from all patients. As for the clinical course of mesothelioma patients during the chemotherapy, the clinical data was retrospectively obtained, and the effectiveness of treatment was evaluated by guidelines for response evaluation criteria in solid tumor (RECIST)[22].

Table 1 Clinical characteristics of patients

1. Mesothelioma patients (n=42)		
Age	mean ± SD	63.5 ± 8.3
	range	47 - 83
Gender	Female	9
	Male	33
Histological subtype	Epithelioid	34
	Biphasic	3
	Sarcomatoid	3
	Desmoplastic	2
Stage	I	5
	II	5
	III	13
	IV	16
	unknown	3
2. Patients without mesothelioma (n=522)		
Age	mean ± SD	64.3 ± 11.1
	range	25 - 92
Gender	Female	101
	Male	421

2. Immunohistochemistry of ERC in mesothelioma

To evaluate the expression status of ERC in mesothelioma tissue, we performed immunohistochemistry of mesothelioma tissue by using mouse monoclonal anti-C-ERC antibody 22A31 (#10357, Immuno-Biological Laboratories (IBL), Fujioka, Gunma, Japan) as a primary antibody. Tissue sections with 4-μm thickness were prepared from formalin fixed, paraffin embedded specimens of mesothelioma obtained by surgical resection or biopsy. After deparaffinization, the tissues sections were heated in 10mM citrate buffer (pH 6.0) for antigen retrieval and treated with 3% hydrogen peroxide. They were blocked with 5% normal goat serum and incubated with 2μg/mL 22A31 in Tris-buffered saline with 0.1% Tween 20 (TBS-T) at room temperature for 180 minutes. After washing with PBS-T, the specimens were incubated with EnVision+ System-HRP labeled polymer conjugated to goat anti-mouse immunoglobulins (DAKO K4001, Agilent Pathology Solutions, Santa Clara, CA, USA), at room temperature for 60 minutes. Finally, the slides were incubated with 3,3-diaminobenzidine (DAB) at room temperature for 3 min. Two pathologists observed findings and evaluated the percentage of ERC-positive area that was expressed as ERC-positive rate (%).

3. Enzyme-linked immunosorbent assay (ELISA) of serum N-ERC or C-ERC

Serum levels of N-ERC and C-ERC were determined by sandwich ELISA systems described previously[12, 23] with some modifications. Briefly, as for detection of N-ERC, two anti-N-ERC antibodies, monoclonal antibody (MoAb) 7E7[11] and horseradish peroxidase (HRP)-conjugated MoAb 16K16[12] were used as capture- and detection-antibodies respectively. As for detection of C-ERC, two anti-C-ERC antibodies, polyclonal antibody (PoAb) anti-C-

ERC6[23] and HRP-conjugated PoAb anti-C-ERC[23] were used as capture- and detection-antibodies respectively. Dilution buffer for serum and detection antibody was 1% bovine serum albumin (BSA) in phosphate-buffered saline with 0.05% Tween 20 (PBS-T). Washing buffer was PBS-T. Diluted serum 100μL was loaded on each well coated with a capture-antibody and incubated at 37°C for 1 hour. After washing, 100μL of detection-antibody solution was added and incubated at 4°C for 30 minutes. After washing, for colorization, 100μL of tetramethylbenzidine solution (#19903, Immuno-Biological Laboratory, Fujioka, Gunma, Japan) was added and incubated at room temperature for 30 min in the dark place. Color development was stopped by 100μL of 1 N H_2SO_4. Absorbance of the solution at 450nm was measured in an ELISA reader (E-Max, Molecular Devices, Sunnyvale, CA, USA). The concentration of N- or C-ERC was determined by the standard curve derived from purified N- or C-ERC proteins[12, 23]. Because of the outlying values of C-ERC in cases 28 and 294, and of N-ERC in a case 220 shown in Table 2, these three cases are removed from the further analyses.

4. Definition of N-higher and C-higher patients

As shown in Tables 2 and 3, some patients showed N-ERC higher than C-ERC, and the others showed the opposite tendency. We defined N-higher patients whose N-ERC values were more than twice higher than C-ERC, and similarly we defined C-higher patients showing C-ERC more than twice higher than N-ERC. In Tables 2 and 3, C-higher patients are shown in dark gray, N-higher ones are shown in white, and the others are shown in light gray backgrounds. Then we examined the relationship of N- or C-higher status and the clinical parameters.

5. Quantification of the ERC-positive volume of mesothelioma

We tried to clarify the relationships between the amount of ERC expressed in mesothelioma and the serum levels of N- or C-ERC. As an indicator of the amount of ERC protein in mesothelioma, we defined the ERC-positive volume (mL), as shown in the following formula.

ERC-positive volume (mL) = mesothelioma volume (mL) x ERC-positive rate (%)

Mesothelioma volume was calculated in 13 patients whose image data of mesothelioma were available by CT or macroscopic pictures of surgical specimens. These 13 cases included 11 epithelioid- and 2 biphasic-types. By using ImageJ software[24 25], we set region of interest (ROI) by drawing the circumference of mesothelioma on CT axial image of a 5-mm thick slice and calculated the area of ROI. The area (mm^2) was multiplied by thickness (5 mm) to induce the volume (mL) of mesothelioma in each slice, and they were summed up to create tumor volume (mL) of whole mesothelioma. In cases in which the macroscopic pictures of surgical specimens were available, ROI was drawn around mesothelioma in each slice. Volume of whole mesothelioma was calculated by a same way as in the cases with CT images. Then we calculated ERC-positive volume (mL) by multiplying mesothelioma volume and ERC-positive rate (%) based on the results of immunohistochemistry in mesothelioma.

6. Clinical data

We evaluated the relationships between the serum levels of N- or C-ERC and clinical factors, such as age, gender and status relating to anemia (Hemoglobin [g/dL], Hb), inflammation (C-reactive protein [mg/dL], CRP), liver damages (alanine aminotransferase [IU/L], ALT), kidney function (Creatinine [mg/dL], Cre), nutrition (Albumin [g/dL], Alb), platelets count ([x104/μL], Plt), and diabetes (Hemoglobin A1c [%], HbA1c).

7. Statistical analysis

All data were analyzed with SAS version 9.4 (SAS Institute, Cary, NC, USA). To compare serum N-/C-ERC levels between mesothelioma patients and those without mesothelioma, t-test was used. Pearson's correlation coefficient test was used to examine the correlation of serum N-ERC levels and C-ERC levels, serum N-/C-ERC levels and the ERC-positive volume in mesothelioma, and serum N-/C-ERC and clinical parameters. We considered that two factors are positively correlated when $r > 0.40$ and $p < 0.05$. Further, serum levels of N-/C-ERC between male and female, and clinical parameters between N-higher and C-higher patients were analyzed by t-test. The relationship between gender and N-/C-higher status was analyzed by chi-square test. A value of $p < 0.05$ was considered statistically significant.

Table 2 Serum levels [ng/mL] of N-ERC (N) and C-ERC (C) in 522 patients without mesothelioma

case	N	C	case	N	C	case	N	C	case	N	C
1	4.5	2.72	67	3.8	3.26	133	4.07	1.09	199	4.92	2.07
2	4.05	2.04	68	2.11	3.11	134	2.15	1.26	200	1.08	3.25
3	4.6	2.31	69	5.98	3.3	135	3.74	2.15	201	2.13	1.28
4	4.84	2.15	70	0.55	0.78	136	3.83	3.47	202	1.39	0.67
5	3.14	1.4	71	4	4.41	137	4.16	4.2	203	3.12	3.69
6	7.09	3.06	72	6.32	3.6	138	7.45	1.54	204	0.79	0.94
7	2.48	0.7	73	0.99	0.76	139	4.92	1	205	0.72	0.84
8	5.55	1.52	74	6.18	0.72	140	0.93	0.97	206	8.17	1.01
9	2.04	1.08	75	11.8	5.27	141	1.95	1.33	207	1.72	1.5
10	2.97	1.5	76	8.3	3.68	142	1.31	1.21	208	2.21	6.6
11	3.74	3.9	77	1.73	2.58	143	1.69	0.73	209	1.8	1.95
12	2.76	0.92	78	4.43	1.45	144	1.83	0.98	210	2.62	4.03
13	3.86	1.59	79	1.41	0.4	145	3.59	2.07	211	1.86	2.3
14	68	30.9	80	0.85	0.53	146	4.51	1.42	212	2.4	3.14
15	3.54	3.29	81	4.52	2.78	147	5.25	2.03	213	2.2	1.86
16	1.81	0.9	82	2.43	1.57	148	3.26	3.06	214	1.51	1.48
17	7.2	4.22	83	3.99	3.48	149	1.62	0.8	215	1.9	1.66
18	2.04	2.19	84	2.11	4.38	150	5.98	3.62	216	2.19	2.91
19	1.34	0.72	85	5.06	3.39	151	4.53	3.89	217	0.4	0.74
20	2.39	0.5	86	0.68	1.08	152	5.99	1.33	218	2.34	2.18
21	3.75	2.75	87	1.02	1.25	153	4.42	5.18	219	2.4	4.76
22	2.03	1.38	88	0.61	0.84	154	1.75	0.91	220	235	71.4
23	1.58	0.82	89	2.06	1.1	155	1.31	0.41	221	1.96	2.9
24	2.88	1.83	90	2.86	7.45	156	5.32	1.98	222	1.3	6.11
25	1.54	0.45	91	3.59	1.57	157	11.1	5.87	223	1.77	3.96
26	5.29	2.58	92	3.63	2.87	158	1.93	0.52	224	33.1	79.9
27	2.19	0.95	93	2.26	6.04	159	3.86	2.69	225	0.75	2.01
28	46.8	301	94	5.68	3.2	160	1.52	0.54	226	11.6	5.53
29	0.66	1.03	95	10.1	18.7	161	4	5.44	227	3.96	2.68
30	1.19	3.18	96	4.66	4.22	162	5.64	8.03	228	6.05	7.36
31	1.16	1.27	97	5.9	2.92	163	6.67	3.03	229	4.46	6.68
32	2.09	2.87	98	1.32	1.46	164	2.38	1.06	230	1.2	1.66
33	1.9	1.38	99	0.76	0.79	165	1.36	1.94	231	5.22	1.92
34	1.91	4.9	100	1.81	2.91	166	1.2	0.66	232	0.82	1.5
35	4.03	3.03	101	2.96	1.52	167	1.47	0.56	233	2.06	2.64
36	1.29	2.14	102	10.4	17.5	168	1.16	1.28	234	1.89	6.46
37	1.68	1.96	103	0.87	2.46	169	N/D	0.38	235	24.1	20
38	1.65	1	104	2.02	1	170	3.6	0.72	236	1.94	2.45
39	2.36	3.05	105	1.95	2.41	171	32	5.98	237	1.35	2.22
40	1.91	1.62	106	1.38	2.58	172	7.42	1.19	238	2.04	2.15
41	4.08	7.8	107	1.28	0.96	173	3.1	3.41	239	0.84	0.68
42	2.94	1.34	108	0.76	0.78	174	1.98	1.14	240	1.62	5.21
43	4.51	3.78	109	3.76	1.43	175	1.92	1.27	241	0.63	1.09
44	2.04	2.58	110	13.5	2.57	176	1.5	1.28	242	0.66	1.39
45	1.36	0.48	111	1.26	0.77	177	1.21	1.26	243	1.92	2.82
46	2.65	1.01	112	9.76	3.47	178	2.62	1.52	244	0.92	1.45
47	2.02	1.67	113	1.86	1.13	179	1.82	1.04	245	0.95	1.39
48	8.42	3.7	114	5.69	1.57	180	4.58	5.33	246	1.38	7.45
49	5.63	2.43	115	4.07	2.63	181	0.01	0.64	247	0.98	1.56
50	1.96	1.45	116	4.2	6.8	182	1.15	1.74	248	0.69	1.42
51	4.76	2.82	117	1.68	1.91	183	10.2	5.92	249	1.92	1
52	2.42	0.94	118	2.2	2.76	184	1.97	2.4	250	2.5	1.9
53	1.8	1.95	119	2.62	1.68	185	1.65	1.18	251	1.7	0.73
54	1	1.79	120	4.06	1.84	186	2.44	2.22	252	11.4	3.49
55	1.5	1.61	121	1.88	0.93	187	4.86	2.41	253	3.23	2.38
56	1.26	2.1	122	5.84	2.57	188	2.55	1.44	254	3.22	1.88
57	2.52	3.55	123	4.86	2.6	189	5.98	3.22	255	1.13	2.5
58	1.02	4.82	124	2.7	3.78	190	0.94	0.48	256	3.55	5.54
59	1.38	1.55	125	3.66	1.88	191	9.38	8.64	257	5.02	34.1
60	0.79	0.52	126	5.86	3.86	192	1.05	2.64	258	2.7	2.77
61	6.05	3.24	127	1.88	0.99	193	2.14	0.88	259	1.1	1.7
62	3.26	6.08	128	0.85	0.36	194	2.32	1.8	260	2.1	1.34
63	6.81	1.41	129	17.4	3.65	195	7.06	2.78	261	1.31	2.1
64	1.32	1.16	130	3.82	1.82	196	2.28	2.95	262	1.13	1.36
65	2.38	5.06	131	4.68	2.09	197	1	1.74	263	35	40.9
66	1.17	1.73	132	4.67	3.28	198	3.29	1.31	264	8.72	18.9

Continue to the next page.

Table 2 (continued)

case	N	C
265	8.06	6.32
266	1.3	1.98
267	3.48	2.87
268	4.34	3.88
269	1.8	1.53
270	1.99	2.13
271	4.24	1.35
272	2	2.75
273	0.84	1.33
274	7.28	6.34
275	1.29	3.6
276	7.71	6.56
277	2.19	2.63
278	40.4	28.5
279	1.99	0.82
280	2.38	2.81
281	1.32	0.7
282	1.48	1.27
283	1.81	1.08
284	15.2	7.3
285	3.84	10.6
286	1.28	0.69
287	0.86	0.44
288	0.59	0.71
289	1.48	0.86
290	2.16	1.33
291	5.22	2.34
292	3.6	2.4
293	111	137
294	14.3	508
295	1.35	0.6
296	8.62	3.11
297	1.72	1.59
298	1.96	0.92
299	2.14	2.08
300	1.93	2.48
301	75.2	37.6
302	4.6	2.05
303	21.3	3.47
304	1.69	1.16
305	0.7	0.51
306	1.78	0.97
307	10.1	2.82
308	0.92	1.13
309	1.15	0.49
310	1.31	0.85
311	4.92	3.68
312	1.18	0.95
313	4.63	2.98
314	5.86	22.6
315	3.58	4.02
316	1.49	2
317	5.56	1.1
318	1.41	1.25
319	3.26	7.17
320	1.92	1.62
321	45.5	13.8
322	0.94	0.98
323	2.39	1.9
324	5.81	17.7
325	2.34	4.4
326	2.21	2.05
327	3.1	2.35
328	1.43	0.68
329	1.54	0.82
330	1.98	1.34
331	3.78	3.1
332	10.6	1.62
333	7.33	4.93
334	2.17	4.93
335	1.61	1.46
336	1.38	1.15
337	4.04	2.22
338	2.38	1.69
339	6.82	1.67
340	2.59	2.22
341	8.33	1.76
342	4.01	0.86
343	3.42	2.14
344	1.2	3.25
345	3.69	8.46
346	8.18	0.91
347	2.16	0.22
348	3.05	1.12
349	3.8	2.58
350	3.75	2.72
351	3.28	1.22
352	5.88	4.98
353	5.57	1.57
354	8.96	10.5
355	8.46	1.69
356	1.54	0.58
357	3.16	1.53
358	4.83	2.42
359	1.23	0.4
360	2.07	2.16
361	4.23	3.59
362	5.82	1.67
363	1.15	1.01
364	8.31	9.71
365	4.31	2.69
366	9.22	1.31
367	7.04	2.54
368	6.46	2.7
369	58.2	5.36
370	2.46	1.54
371	5.41	10.5
372	7.66	1.88
373	1.8	1.26
374	1.86	1.1
375	1.2	1.02
376	9.6	7.41
377	9.24	4.66
378	6.44	1
379	7.12	5.14
380	4.18	1.17
381	7.12	2.99
382	9.02	8.46
383	2.88	1
384	13.5	20.9
385	3.8	1.3
386	7.47	2.21
387	14.3	9.3
388	1.82	0.89
389	2.67	1.56
390	4.65	3.2
391	3.46	0.78
392	3.85	1.89
393	3.41	0.63
394	2.66	1.28
395	2.68	0.8
396	3.53	1.97
397	10.1	7.01
398	8.38	4.03
399	7.84	1.32
400	2	0.7
401	3.07	7.46
402	9.34	2.69
403	23.2	222
404	7.04	4.93
405	5.09	1.26
406	4.2	4.94
407	8.9	10.4
408	5.94	1.03
409	4.26	1.21
410	4.93	2.42
411	5.32	21.3
412	14.3	3.98
413	3.64	1.15
414	10.5	24.9
415	2.87	1.11
416	3.89	1
417	6.29	2.35
418	6.22	2.96
419	8.27	1.97
420	3.96	0.67
421	3.26	2.86
422	3.46	0.64
423	7.3	3.98
424	8.49	8.58
425	6.04	3.68
426	2.51	0.7
427	7.16	1.29
428	4.3	2.96
429	2.64	1.9
430	3.65	3.26
431	5.84	1.14
432	6.72	0.97
433	3.44	2.53
434	86	27.3
435	1.23	0.44
436	2.91	3.38
437	25.3	15.7
438	2.49	0.69
439	19.6	2.83
440	1.95	0.53
441	4.95	2.1
442	7.41	0.74
443	3.95	0.61
444	2.13	0.5
445	6.99	1.23
446	10.7	17
447	3.43	5.84
448	7.36	1.87
449	2.68	1.22
450	4.61	2.27
451	16.7	16.5
452	3.49	5.12
453	8	4.72
454	1.9	1.08
455	8.27	2.9
456	8.19	1.29
457	6.85	22.4
458	6.32	0.83
459	5.76	0.8
460	7.47	1.21
461	9.11	11.6
462	6.7	4.06
463	6.55	3.14
464	6.69	0.72
465	4	0.46
466	5.69	0.64
467	17.5	14.4
468	2.88	3.01
469	7.57	0.72
470	11.3	1.2
471	8.94	1.69
472	8	3.18
473	6.95	1.08
474	1.41	0.54
475	4.33	2.61
476	5.58	4.19
477	6.06	2.2
478	3.35	2.69
479	3.35	2.37
480	1.71	0.41
481	4.18	1.24
482	8.06	2.54
483	4.7	0.71
484	6.84	5.91
485	7.54	1.26
486	2.72	0.94
487	6.4	1.02
488	7.12	1.09
489	1.85	1.54
490	5.46	0.98
491	54.6	2.33
492	3.27	0.6
493	7.67	0.59
494	5.08	5.29
495	6.43	4.12
496	3.68	1.37
497	3.93	2.29
498	2.43	4.26
499	3.72	4.54
500	5.07	10.9
501	9.68	2.79
502	1.4	0.52
503	2.04	1.24
504	6.67	2.5
505	3.31	2.45
506	9.09	4.5
507	2.99	0.95
508	0.76	2.08
509	8.87	3.66
510	50	35.2
511	1.77	2.29
512	5.33	2.56
513	2.94	13.8
514	2.13	2.98
515	3.66	1.14
516	3.19	1.85
517	4.5	0.82
518	0.84	0.98
519	3.82	2.81
520	1.56	2.19
521	4.55	1.41
522	2.69	2.54

C-higher patients (C > N x 2) are shown in dark gray, N-higher ones (N > C x 2) are shown in white, and the others are shown in light gray background. N/D, not determined (case 169). Note that Cases 28, 220 and 294 are removed from the further analysis because of outlying values.

Table 3 Serum levels [ng/mL] of N-ERC (N) and C-ERC (C) in 42 mesothelioma patients

case	N	C	case	N	C
1	21.38	2.7	22	3.44	3.18
2	67.97	30.85	23	11.58	5.53
3	4.5	0.78	24	45.49	6.4
4	5.98	3.22	25	50.9	99.33
5	9.2	5.02	26	10.16	7.64
6	31.26	7.16	27	15.2	7.3
7	25.23	23.23	28	2.03	1.38
8	10.64	1.62	29	6.84	4.25
9	8.33	1.76	30	2.06	1.1
10	111.36	136.96	31	59.52	180.74
11	6.82	1.67	32	1.4	0.95
12	7.76	15.87	33	56.83	36.74
13	56.9	7.2	34	21.28	6.14
14	70.53	20.67	35	1.2	3.25
15	2.2	3.38	36	9.34	2.69
16	2.2	1.86	37	1.95	2.26
17	4.24	1.35	38	1.98	1.14
18	4.18	1.17	39	2.02	1
19	18.34	5.09	40	5.08	5.29
20	6.18	0.72	41	1.85	2.36
21	3.86	3.62	42	8.12	4.8

C-higher patients (C > N x 2) are shown in dark gray, N-higher ones (N > C x 2) are shown in white, and the others are shown in light gray.

Results

As expected, serum levels of N- and C-ERC were higher in mesothelioma patients than in those without mesothelioma (N-ERC; 19.0 ± 24.7 [n = 42] vs 5.4 ± 9.5 [n = 518], $p < 0.05$, C-ERC; 15.7 ± 36.2 [n = 42] vs 3.8 ± 8.4 [n = 518], $p < 0.05$). N- and C-ERC levels were positively correlated both in mesothelioma patients (Figure 2A) and those without mesothelioma (Figure 2B), with correlation coefficients 0.71 and 0.54 in mesothelioma patients and those without mesothelioma, respectively.

In 13 mesothelioma patients whose image data of the lesion was available, we checked the correlation between the serum levels of N- or C-ERC and the amount of ERC in mesothelioma that is expressed as the ERC-positive volume (mL). Serum levels of C-ERC correlated positively to the ERC-positive volume in mesothelioma (Figure 3B), but those of N-ERC did not (Figure 3A). Their raw data is shown in Supplementary Table 1.

In patients without mesothelioma, we examined the relationship between the serum levels of N- or C-ERC and the clinical parameters such as age, gender and status relating to anemia, inflammation, liver damages, kidney function, nutrition, platelets count, and diabetes, as described in Materials and Methods. As a result, serum creatinine levels, as the marker of renal function, correlated positively to serum levels of N-ERC (Figure 4A), but not to those of C-ERC (Figure 4B). All the other clinical parameters examined in this study did not have any correlation to either of C- or N-ERC (Supplementary Figure 2).

Serum levels of N-/C-ERC in 522 patients without mesothelioma and 42 mesothelioma patients are listed in Tables 2 and 3, respectively. In some patients C-ERC was higher than N-ERC, and in the others N-ERC was higher than C-ERC. As described in

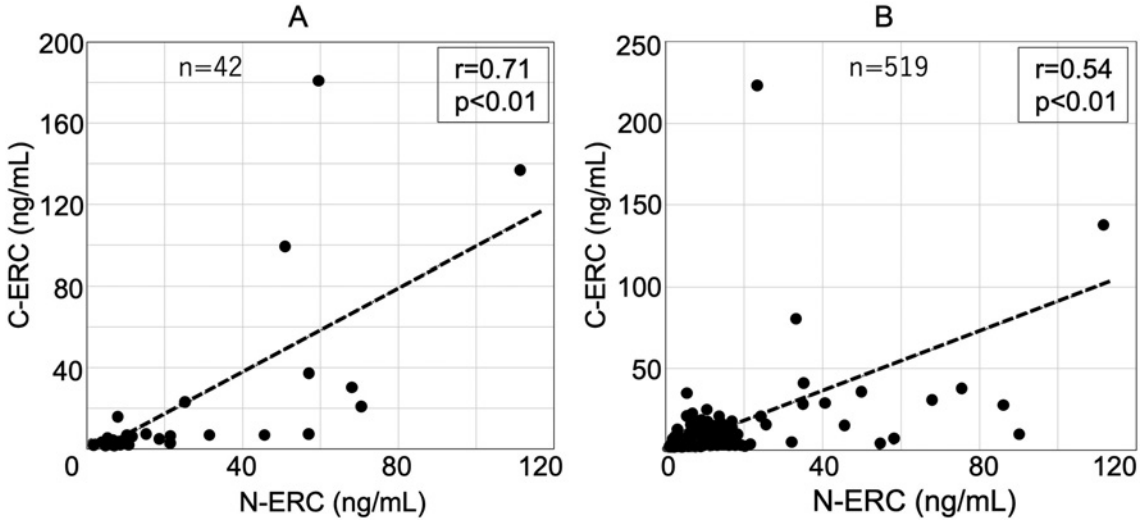


Figure 2 Relationship between serum N- and C-ERC in 42 mesothelioma patients (A) and 519 outpatients without mesothelioma in asbestos/mesothelioma clinic (B). Serum levels of N-ERC were positively correlated to those of C-ERC both in mesothelioma patients (A) and those without mesothelioma (B).

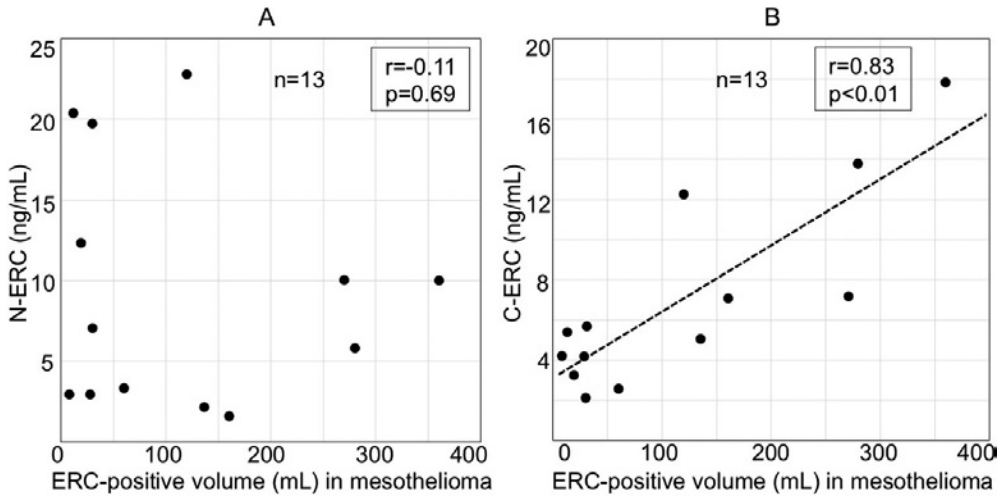


Figure 3 Relationship between ERC-positive volume (mL) in mesothelioma and serum levels of N-ERC (A) and C-ERC (B). Serum levels of C-ERC correlated to ERC-positive volume (mL) in mesothelioma (B), but that of N-ERC did not (A). ERC-positive volume (ml) was calculated by multiplying tumor volumes (mL) and ERC-positive area (%) in mesothelioma. n=13.

Supplementary Table 1 Relationship between N- or C-ERC levels in serum and the expression of ERC in mesothelioma

Case	in serum		in mesothelioma		
			(A)	(B)	(C)
	N-ERC	C-ERC	ERC-positive area	Tumor volume	ERC-positive volume
	(ng/ml)		(%)	(ml)	
1	20.34	5.41	10	130	13
2	12.33	3.23	10	190	19
3	7.09	5.68	10	300	30
4	2.94	4.19	10	280	28
5	5.87	13.7	70	400	280
6	22.8	12.29	80	150	120
7	10	17.74	90	400	360
8	19.74	2.1	20	150	30
9	3.34	2.61	20	300	60
10	2.22	5.06	80	170	136
11	9.99	7.14	90	300	270
12	1.62	7.07	20	800	160
13	2.98	4.18	10	80	8

(C) = (A) x (B). Cases 1-11 are epithelioid and cases 12, 13 are biphasic type mesothelioma.

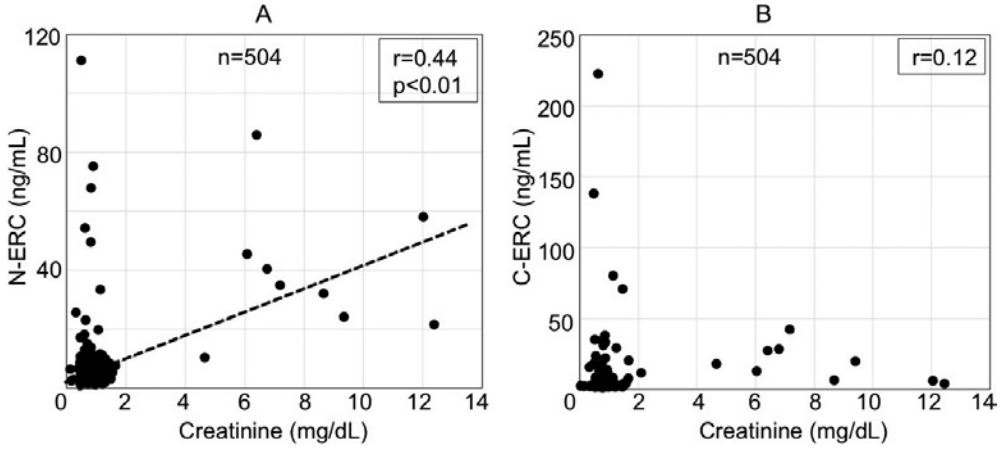
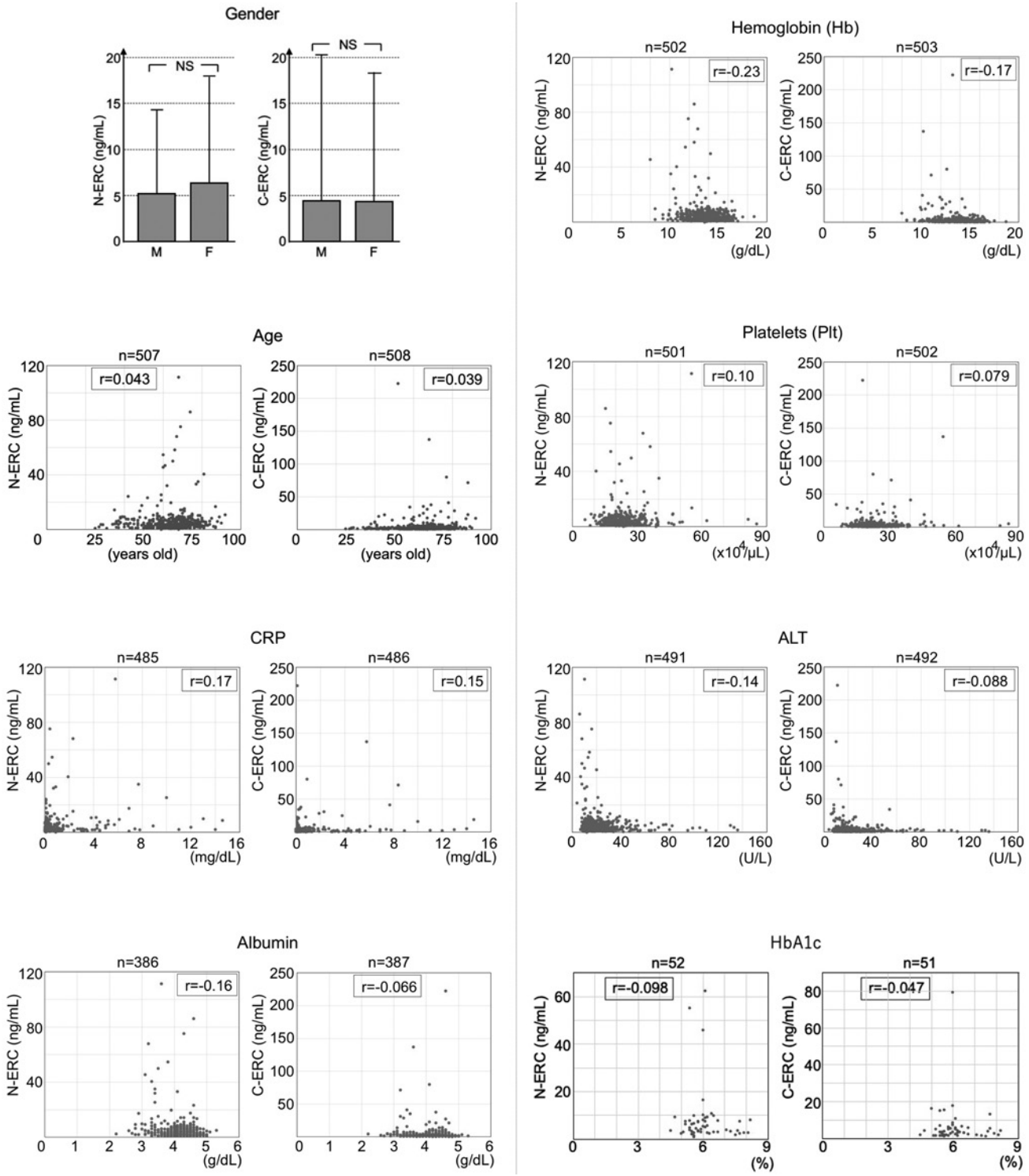


Figure 4 Relationship between serum levels of creatinine and N-ERC (A) or C-ERC (B) in 504 patients without mesothelioma. Serum levels of creatinine was positively correlated to N-ERC.



Supplementary Figure 2 Relationship between serum levels of N- or C-ERC and clinical factors in patients without mesothelioma. Gender ; To compare N-/C-ERC levels between male and females, t-test was used. There was no significant difference of N-/C-ERC between male and female. NS, not significant. Age, CRP, Albumin, Hemoglobin, Platelets, ALT, HbA1c; Pearson's correlation coefficient test was used to examine the correlation of these parameters and serum N-/C-ERC levels. No correlation was observed between N-/C-ERC and these parameters. We considered that two factors are positively correlated when $r > 0.40$ and $p < 0.05$.

Table 4 Clinical factors and N- or C-ERC higher status in patients without mesothelioma

Clinical factors	N-higher	C-higher	p-value
Age (years)	64.0 ± 0.64 (184)	64.7 ± 0.76 (40)	0.51
CRP (mg/dL)	0.91 ± 0.15 (176)	1.32 ± 0.23 (40)	0.12
Hemoglobin (g/dL)	13.7 ± 0.10 (183)	13.7 ± 0.12 (39)	0.94
Platelets (x10^4/ μ L)	23.3 ± 0.50 (182)	24.4 ± 0.62 (40)	0.16
Creatinine (mg/dL)	0.93 ± 0.07 (182)	0.87 ± 0.05 (40)	0.59
Albumin (g/dL)	4.11 ± 0.03 (157)	4.09 ± 0.05 (24)	0.78
ALT (IU/L)	23.8 ± 1.08 (179)	22.8 ± 0.94 (39)	0.63
γ -GTP (IU/L)	45.7 ± 3.7 (170)	50.6 ± 4.6 (38)	0.40

N-higher; N > C x 2. C-higher; C > N x 2. Number of cases are shown in parenthesis.

Table 5 Gender and N- or C-ERC higher status in patients without mesothelioma

Gender	N-higher	C-higher	p-value
Male	142	37	<0.05
Female	42	3	

N-higher; N > C x 2. C-higher; C > N x 2.

Materials and Methods, we defined C-higher (C > N x 2), N-higher (N > C x 2) and the other patients, and they are shown in dark-gray, white, and light-gray backgrounds respectively in Tables 2 and 3. In 522 patients without mesothelioma, the numbers of C-higher and N-higher patients were 43 and 184, respectively. Between these two groups, we compared age, gender and the other clinical parameters. Results showed that no relationship was detected between N- or C-higher states and all clinical factors (Table 4) except for gender. More females than males were included in N-higher group with statistical significance (Table 5).

Figure 5 shows the changes of serum N- or C-ERC in 2 mesothelioma patients who received chemotherapies. Response rates to therapies as indicated by RECIST[16] system are also indicated. Both N- and C-ERC were shown to be reliable markers to reflect the tumor burdens in these two cases, as reported previously by other groups[14 16].

Discussion

In mesothelioma tissues, ERC is localized on cellular membranes (Supplementary Figure 1), and it is detected by anti-C-ERC antibodies. On the contrary, anti-N-ERC antibodies[11, 12, 26], that recognize the internal amino acid sequences of N-ERC and detect N-ERC in the extracellular fluid, cannot make specific signals in any cellular components of mesothelioma (data not shown). These findings suggest that almost all N-ERC molecules are released into the extracellular spaces, and that C-ERC are partially released but some of them are remaining on the cellular membrane. Therefore,

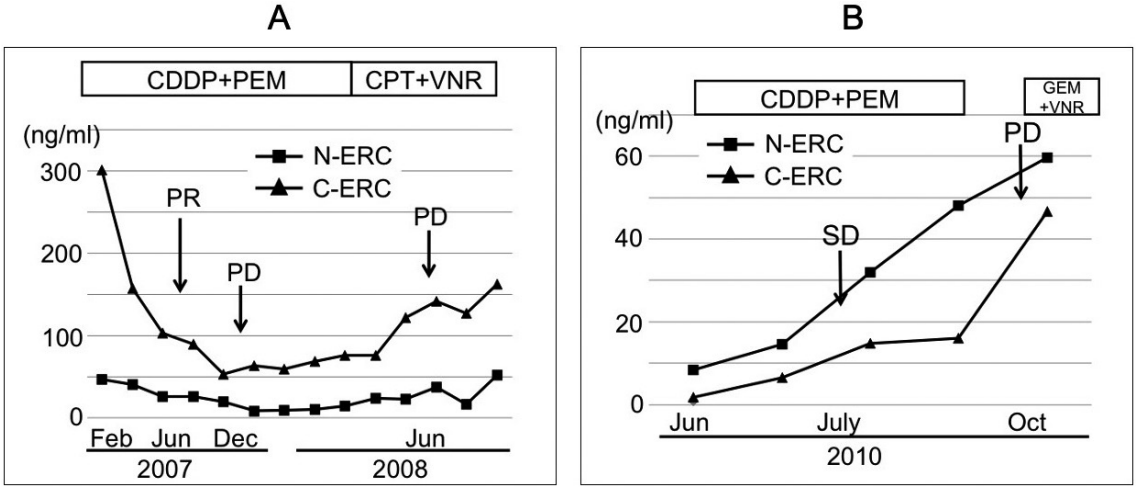


Figure 5 Changes of the serum levels of N- and C-ERC in two mesothelioma patients. Both of N- and C-ERC reflected the tumor burden of mesothelioma in individual patients. (A) The case showing C-ERC consistently higher than N-ERC, (B) The case showing N-ERC consistently higher than C-ERC. PR; partial response, PD; progressive disease, SD; stable disease, CDDP; Cisplatin, PEM; Pemetrexed sodium hydrate, CPT; Camptothecin (Irinotecan hydrochloride hydrate), VNR; Vinorelbine detartrate, GEM; Gemcitabine hydrochloride.

the amount of ERC in mesothelioma is evaluated by IHC using anti-C-ERC antibodies.

Creaney et al.[16] previously reported that serum levels of C-ERC correlated with volume of mesothelioma, and their work supports our result shown in Figure 3B. They, however, just measured volume of mesothelioma and they did not count the expressional state of ERC in mesothelioma. We compared the serum levels of N- or C-ERC and three parameters related to ERC in mesothelioma tissue: (A) tumor volume (ml), or (B) ERC-positive rate (%), or (C) ERC-positive volume [(C) = (A) x (B)]. All three parameters are defined in Materials and Methods. As shown in Supplementary Table 2, serum C-ERC level more significantly associated with ERC-positive volume (ml), than ERC-positive area (%). In our study, the significant relationship was not observed between serum C-ERC and tumor volume, as reported by Creaney et al.[14] possibly because of small number of cases (n=13) in our study. Serum level of N-ERC did not have any significant relationships with these three parameters.

Shiomi et al.[21] previously reported that serum levels of N-ERC are increased in the patients with renal failure. Therefore, in this study, we examined whether N- or C-ERC is influenced by renal functions and by the other clinical factors such as age, gender, inflammatory status, nutritional condition, anemia, liver function, platelets numbers, or diabetes. As shown in Figure 4, serum creatinine level positively correlated with N-ERC, but not with C-ERC, and this result is compatible with the report by Shiomi et al[21]. Both of N- and C-ERC did not have any correlation to the other clinical factors examined in this study (Supplementary Figure 2). N-ERC is identical to megakaryocyte potentiation factor (MPF)[7] that has the activity to simulate megakaryocyte development in murine system[27], although the similar activity has not been reported in human. We studied the relationship between N-ERC and platelets numbers, and we did not find the correlation between them. Shiomi et al.[12] also reported that serum levels of N-ERC is influenced by age. In our data, the elder patients tended to have higher levels of N-ERC, but the correlation was not significant (Supplementary Figure 2).

Multiple studies reported that serum levels of N-ERC[11-14, 17-18, 20] and C-ERC[15-16, 19] reflect the tumor burden of mesothelioma. After the effective chemotherapy or surgical treatments, the serum levels of N-ERC[14] and C-ERC[16] decrease, and similar results are shown in Figure 5A. These findings indicated that both N- and C-ERC are good markers to monitor the status of mesothelioma in the clinical course of the same patients. Our present data (Figure 3) showed that, among different patients, C-ERC reflected the amount of ERC in mesothelioma more accurately than N-ERC, partly because N-ERC was influenced by renal function that is not directly associated with condition of mesothelioma.

It was puzzling for us why some patients showed that N-ERC was higher than C-ERC, and the others showed the opposite tendency. We tried to identify the causes of these phenomenon, but we were not able to find them, except for that N-higher patients included more female than male with statistical significances (Table 5). Renal clearance rate is generally higher in men than in women[28]. If N-ERC is excreted through renal routes, the higher clearance activity of men can explain our finding that N-higher group included more female. This explanation is compatible with the data that serum levels of N-ERC showed a tendency to be higher in female than in male, although there was no statistical significance (Supplementary Figure 2). In a patient shown in Figure 5A, C-ERC was always higher than N-ERC, and the relationship was opposite in a patient in Figure 5B, and these data suggested the possibility that N-higher or C-higher states were determined by some factors intrinsic to each patient. Recently, sex differences in carcinogenesis are being discussed[29], and some hormonal condition may influence N-higher or C-higher states, although they are to be elucidated in future.

In conclusion, our study gave us a caution that we must be careful in the interpretation of serum

Supplementary Table 2 Relationships between N-ERC or C-ERC levels in serum and three indicators (A), (B), (C) in mesothelioma

Indicators in mesothelioma	N-ERC	C-ERC
	p-value	
(A) Tumor volume (ml)	0.11	0.28
(B) ERC-positive rate (%)	0.74	0.0039
(C) ERC-positive volume (ml)	0.69	0.0005

(C) = (A) x (B). Serum C-ERC is more significantly associated with ERC-positive volume (C) than ERC-positive rate (B) or Tumor volume (A). Serum N-ERC is not significantly associated with any of three indicators.

N- and C-ERC values as the marker of mesothelioma among different patients, because N-ERC was influenced by renal functions that are not directly associated with conditions of mesothelioma. These markers are, however, still very valuable to monitor the status of mesothelioma in the same patients.

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Author contributions

AK collected the data, undertook immunohistological studies, and drafted the manuscript. KK, TK, and YS designed this study. SN, AK, and KK performed statistical analysis. LY assisted the analysis of images to calculate the ERC-positive volume of mesothelioma. AA supervised the histological studies. MA performed ELISA to measure serum N- and C-ERC. NO assisted the immunohistochemical study. TS, KT, and KS supported the planning of this study, and AO, TY, and OH supervised this project. KK revised the manuscript. All the authors have read and approved the final version of this manuscript.

Conflicts of interest statement

The Authors declare that there are no conflicts of interest.

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Reports

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Clinical Benefit of Cancer Philosophy Clinic for Cancer Patients Using EQ-5D-5L Scores

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Objective: This study aims to understand the role of Cancer Philosophy Clinic activities among participants and whether participation is correlated to increase in QOL.
Materials and Methods: Among the 150 Cancer Philosophy Clinics, questionnaire surveys were distributed at 28 locations that consented to participating in the study. The data was analyzed based on the respondent's situation and health related Quality of Life (QOL) prior to and after participating in Cancer Philosophy Clinic using the EQ-5D-5L questionnaire (Japanese version) regarding health related QOL prior to and after participating in Cancer Philosophy Clinic.
Results: There were more female participants than male participants; 224 and 76 respectively. 46.5%, or approximately half of all participants in the Cancer Philosophy Clinic were "cancer patients," followed by 17.2% who were "family members of cancer patients," 16.6% who were "not suffering from any diseases," 11.4% who were "suffering from diseases other than cancer" and 3.2% who were classified as "other," who were bereaved family members. 51.7% were "currently receiving treatment, "32.1% were "receiving follow-up medical care, "and 15.3% were "survivors." There was 1 participant who commented, "refusing treatment." Based on an evaluation of QOL using EQ-5D-5L of 184 participants who were participating in the Cancer Philosophy Clinic, an increase in overall average index value from 0.827 to 0.867 was observed after participation compared to prior participation. In particular, there was a significant improvement in "pain/discomfort," "anxiety/depression.
Conclusions: Cancer Philosophy clinic has been found important role in encouraging existing shift.
Key words: cancer philosophy clinic, cancer patients, EQ-5D-5L

Introduction

The population in Japan is aging significantly. As aging progresses, there is greater concern for developing various diseases. Aging is one factor in developing cancer, dementia, cerebrovascular disease, and cardiovascular disease. According to a study by the Ministry of Health, Labour, and Welfare[1)], a breakdown of inpatients and outpatients in 2014 by disease and related health problems found the greatest number of inpatients suffering from "V mental and mobile disability," (265.5 thousand) "XI cardiovascular disease," (240.1 thousand) and "II neoplasm" (144.9 thousand). The greatest number of outpatients was suffering from "XI digestive disease," (1.31 million), "XI cardiovascular disease," (933 thousand), and "XIII musculoskeletal and connective tissue disease," (877.8 thousand. 1) malignant growths, or cancer is the third most common disease among inpatients. Currently, cancer rates are rising and 1 in 2 patients are said to be cancer patients. Cancer is the most common cause of death in Japan.

Cancer patients suffer not only from physical pain but also from psychological pain, mental illness, and spiritual pain[2)]. There are a variety of cases especially among cancer patients varying from those who respond well to cancer treatment, those

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whose condition remains unchanged, and those whose condition worsens; the cancer site, progression, medicine and treatment methods. QOL (Quality of Life) declines frequently especially in cases of progressive cancer and mental and psychological pain. It is clear that there is a tremendous impact on the QOL of patients. Psychological pain excluding pathological mental condition is described as spiritual pain. Many patients suffer from spiritual pain and experience anxiety, denial and despair toward themselves, and feel a tremendous sense of isolation and anger with no outlet.

Cancer Philosophy is a combination of "Political Philosophy," by Shigeru Nanbara (First President of University of Tokyo after the war, 1889–1974) and "Cancer Studies," by Tomizo Yoshida (General Manager of Cancer Research Institute, Professor of Tokyo University, General Manager of Sasaki Laboratory, 1903–1973) proposed by Okio Hino. (Professor of Pathology and Oncology Juntendo University)[3].

Cancer Philosophy Clinic was started as a series of five trials at Juntendo University Hospitals as an interactive outpatient service. There were many cancer patients and patients suffering from mental illness who wished to confide in someone their anxieties and thoughts. There were many participants not only from Tokyo but from other prefectures.

Cancer Philosophy Clinic is a place where patients suffering from anxiety, anger, and isolation, and those in any situation are accepted and supported. Currently there are 150 Cancer Philosophy Clinic locations nationwide, each with a representative. The number of times Cancer Philosophy Clinic is held and capacity vary from location to location. A small group of participants gather around a table to speak and listen over tea. Listeners do not deny what the speaker says, but listen, empathize and provide their opinions and advice based on their personal experiences. For those who cannot speak, participants may quietly support or speak to the person. If a coordinator facilitates, they summarize and present the opinions of participants at each table and sometimes share what was discussed with other tables. Cancer Philosophy Clinic activities are gradually increasing. Needless to say, there is an increasing demand. However, there has been little research on the needs and the role of Cancer Philosophy Clinic. There has been no research done on the participants attributes and the influence Cancer Philosophy Clinic has on increases in health related QOL.

Objective

This study aims to understand the role of Cancer Philosophy Clinic activities among participants and whether participation is correlated to increase in QOL.

Methods

Among the 150 Cancer Philosophy Clinics, questionnaire surveys were distributed at 28 locations that consented to participating in the study. The data was analyzed based on the respondent's situation and health related Quality of Life (QOL) prior to and after participating in Cancer Philosophy Clinic using a EQ-5D-5L questionnaire (Japanese version) regarding health related QOL prior to and after participating in Cancer Philosophy Clinic.

Attribute

1) Age and Gender
2) Presence of disease
3) Situation of Treatment (for cancer patients and those who responded as suffering from diseases other than cancer)
4) Participation in Cancer Philosophy Clinic

Index Value of QOL

Health related QOL prior to and after participation in Cancer Philosophy Clinic was measured using EQ-5D-5L (Japanese version).

EQ-5D-5L is a standardized measure of health status which scores "mobility," "self-care," "usual activities," "pain/discomfort," "anxiety/depression" on a 5-level system.

Period

3 months from June 2018 to August 2018.

Results

Attribute

1) Age and Gender (Figure 1)

There were more female participants than male participants; 224 and 76 respectively. The greatest number of participants was in their fifties, accounting for 32.4% (99 participants) of total responses, followed

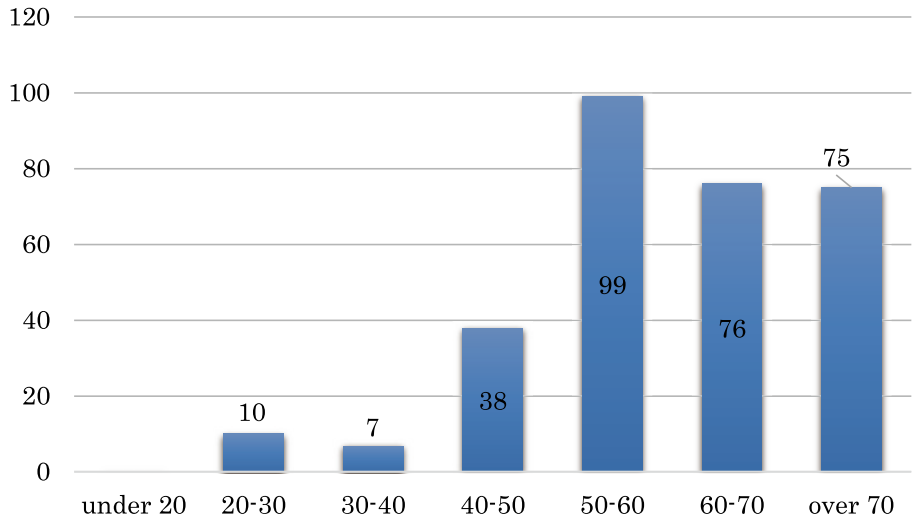

Figure 1 Age
The greatest number of participants was in their fifties, accounting for 32.4% (99 participants) of total responses, followed by 24.99% (76 participants) in their sixties, 24.5% (75 participants) in their seventies, 12.4% (38 participants) in their forties, 3.2% (10 participants) in their twenties and 2.2% (7 participants) in their thirties, with no participants under the age of 20.

by 24.99% (76 participants) in their sixties, 24.5% (75 participants) in their seventies, 12.4% (38 participants) in their forties, 3.2% (10 participants) in their twenties and 2.2% (7 participants) in their thirties, with no participants under the age of 20.

2) Presence of disease (Figure 2)

46.5% (143 participants), or approximately half of all participants in the Cancer Philosophy Clinic were "cancer patients," followed by 17.2% (53 participants) who were "family members of cancer patients," 16.6% (51 participants) who were "not suffering from any diseases," 11.4% (35 participants) who were "suffering from diseases other than cancer" and 3.2% (10 participants) who were classified as "other," who were bereaved family members.

3) Situation of Treatment (Figure 3)

Among the 143 respondents who identified as "cancer patients" or "family members of cancer patients," 51.7% (74 participants) were "currently receiving treatment, "32.1% (46 participants) were "receiving follow-up medical care, "and 15.3% (22 participants) were "survivors." There was 1 participant who commented, "refusing treatment."

4) Participation in Cancer Philosophy Clinic (Figure 4)

21.9% (67 participants) "participated for the first time," 9.1% (28 participants) "participated for the second time," and 68.7% (210 participants) "participated three or more times," indicating that there were many participants who had participated

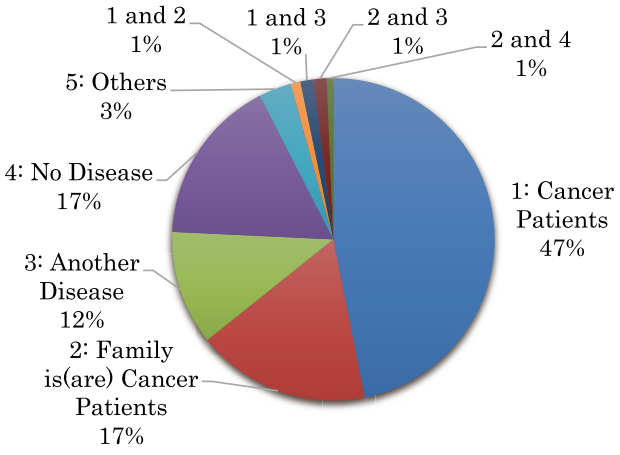

Figure 2 The Presence of Cancer
46.5% (143 participants), or approximately half of all participants in the Cancer Philosophy Clinic were "cancer patients," followed by 17.2% (53 participants) who were "family members of cancer patients," 16.6% (51 participants) who were "not suffering from any diseases," 11.4% (35 participants) who were "suffering from diseases other than cancer" and 3.2% (10 participants) who were classified as "other," who were bereaved family members.

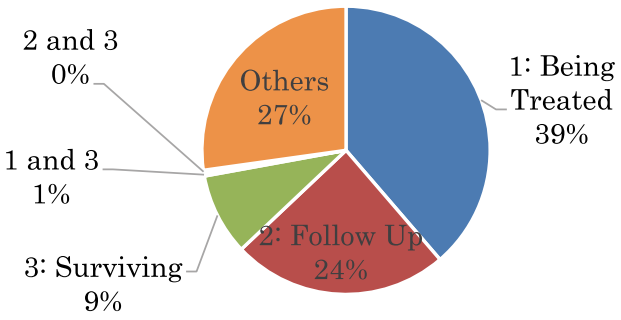

Figure 3 Situation of Treatment
Among the 143 respondents who identified as "cancer patients" or "family members of cancer patients," 51.7% (74 participants) were "currently receiving treatment, "32.1% (46 participants) were "receiving follow-up medical care, "and 15.3% (22 participants) were "survivors." There was 1 participant who commented, "refusing treatment."

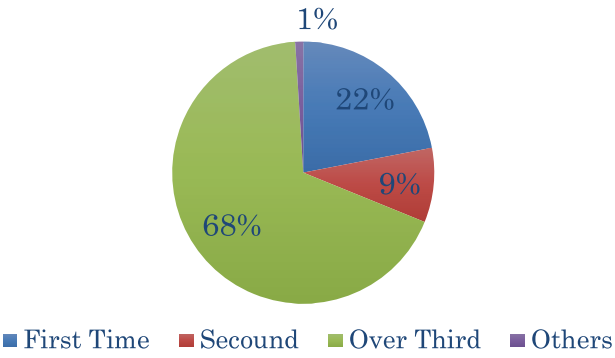

Figure 4 Number of Participated in Cancer Philosophy Clinic
21.9% (67 participants) "participated for the first time," 9.1% (28 participants) "participated for the second time," and 68.7% (210 participants) "participated three or more times," indicating that there were many participants who had participated multiple times.

multiple times.

Based on an evaluation of QOL using EQ-5D-5L (Japanese edition) of 184 participants who were "cancer patients," "suffering from diseases other than cancer," or both participating in the Cancer Philosophy Clinic, an increase in overall average index value from 0.827 to 0.867 was observed after participation compared to prior participation. Among the 187 participants, change in QOL was observed in 47 participants, of which an increase in QOL was observed in 39 participants, and a decrease in QOL in 8 participants. In the details, 46 participants of the 47 participants changed and good improvement was confirmed. In particular, there was a significant improvement in "pain/discomfort," "anxiety/depression" (Figure 5).

Discussion

Attribute

Participants in Cancer Philosophy Clinic in their fifties account for 32.4% of all participants, and 81.8% of all participants including those in their sixties and seventies. According to "Cancer registration and statistics" data from the National Cancer Center Information Service in 2014, cancer rates increase past the age of 50. As such, more people participate in Cancer Philosophy Clinic. In addition, women are more interdependent and tend to participate more actively in their communities than men[4].

Approximately half of all participants are "cancer patients" and suffer from mental and psychological distress from being diagnosed with cancer. It is clear that emotional support beyond physical treat-

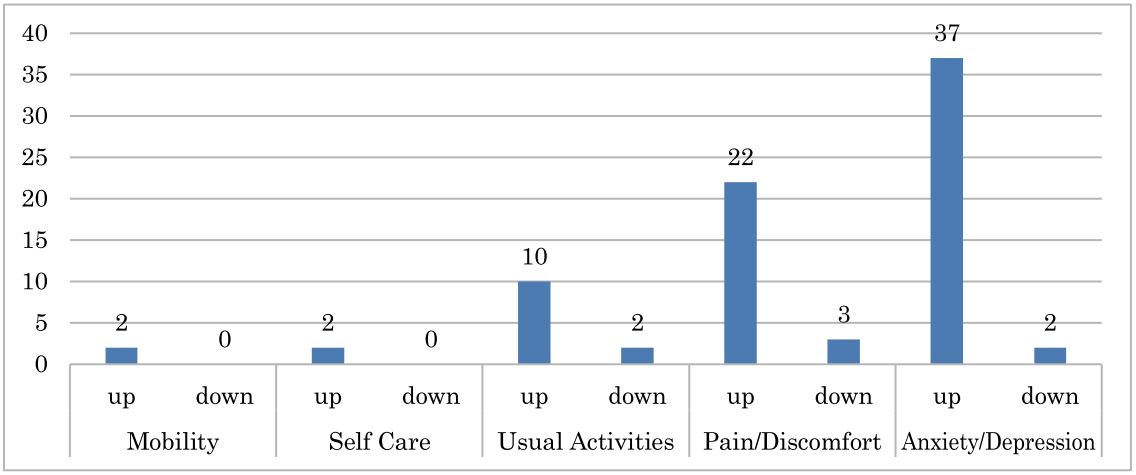

Figure 5 Changes after Participation 5 Scores of 47 Participants
46 participants of the 47 participants changed and good improvement was confirmed each 5 scores.

ment and support from doctors at hospitals is necessary. Nowadays, "cancer" does not automatically equate to "death," but is rather considered a treatable disease. Nonetheless, one may become more aware of "death" in many cases. Depending on the progression of an illness, treatment may be difficult in some cases. It is known that there is a five-stage model in accepting death and dying[5].

In the first stage of denial and isolation, a person who is given a diagnosis of terminal illness is in shock and disbelief, and often isolates oneself to avoid the situation. In the second stage of anger, they may start to ask, "Why me?" and experience strong resistance. In the third stage of bargaining, they accept that they are dying, but try to bargain to avoid death from a desire to live a little longer. In the fourth stage of depression, they experience sadness, despair, and at times a feeling emptiness and accept that death is unavoidable. In the fifth stage of acceptance, they overcome the denial, avoidance, and feeing of emptiness experienced in earlier stages. It is a stage of peaceful resolution that death will occur. In this stage, a person quietly reflects upon their life and regains emotional peace and calm. At Cancer Philosophy Clinic, participants in various stages can gather and share their thoughts over tea with those in similar situations.

17.2% of participants were "family members of cancer patients." When a family member suffers from cancer, there is a deep sadness and anxiety felt as if it were one's personal situation. Many of these participants express concern and anxiety because they are unsure how to interact with the family member. At Cancer Philosophy Clinic, participants can listen to candid opinions of cancer patients and those suffering from other diseases that are difficult to treat. It is a space where they can confide in others their concern and anxiety. It is thought that having someone listen leads to mental stability. The sadness and loneliness experienced by the loss of family, friends, and close ones is immeasurable. The high number of bereaved family members indicates that Cancer Philosophy Clinic helps ease sadness and anger and serves the purpose of providing grief care.

Among the 307 respondents, 143 participants were "cancer patients," of which 51.7% were "currently receiving treatment." It is thought that participation leads to a broader perspective regarding the availability of alternative treatment options or perspectives, as well as whether the current treatment and its direction are appropriate. At Cancer Philosophy Clinic, there are many participants who question the direction of their treatment and are considering seeking a second opinion. Cancer Philosophy Clinic is a forum to gather valuable information for those currently receiving treatment.

68.7% of participants have participated in Cancer Philosophy Clinic three or more times indicated a high number of participants who have participated multiple times. It is thought that visiting Cancer Philosophy Clinic several times and talking to those in similar situations leads to physical and mental stability. In addition, for those who are in poor condition and unable to leave the house, services such as online, letters and messages need to be enhanced.

Health related QOL

The QOL of 184 "cancer patients," "those suffering from diseases other than cancer," or both was scored using EQ-5D-5L (Japanese version). EQ-5D was developed by EuroQol, a research group established in 1978. EQ-5D-5L is a new version that was later developed which can be used as a quantitative measure of health related QOL. The system is comprised of five dimensions, which the patient is asked to rate his or her health on five levels. A conversion table is used to describe the patient's state of health[6].

An increase in overall average index value from 0.827 to 0.867 was observed after participation compared to prior participation. Change in QOL was observed in 47 participants, of which an increase in QOL was observed in 39 participants, and a decrease in QOL in 8 participants.

The respondents of this survey who were able to participate in Cancer Philosophy Clinic, therefore they were under treatment but had relatively preserved or relaxed ADL. As a result, index value averaged from 0.827 before participation to 0.867 after participation. Another study found that the epidemiological survey of nonspecific neck pain in the general population using EQ-5D, it can be said that the QOL of the group "with neck pain averaged 0.828" and that of the group "without neck pain averaged 0.919[7]". In another survey, the QOL

assessment for postoperative patients of colorectal cancer, the score was "0.867[8]", and a large-scale survey on the impact of chronic pain on QOL, "0.71 with chronic pain" and "0.89 without chronic pain" were found to preserve quality of life better than those with chronic pain[9].

Half of all participants of Cancer Philosophy Clinic are "cancer patients," of which half are "currently receiving treatment." Normally, it can be inferred that cancer physically and mentally debilitates patients, and thus a decrease in QOL score could be predicted.

Changes in scores of the five dimensions: "mobility," "pain/discomfort," "self-care," "usual activities," and "anxiety/depression" were observed.

As a result, there were a significant number of participants who saw an improvement in "anxiety/depression." We found that participating in Cancer Philosophy Clinic leads to easing anxiety and depression. It could be said that Cancer Philosophy Clinic greatly contributes to easing mental and emotional distress.

On the other hand, a study of the 8 participants whose QOL declined indicated that there were many cases where "usual activities," "pain/discomfort" worsened. It is thought that the increase in pain and discomfort caused by diseases limits the patient's daily activities, which leads to increased anxiety.

Conclusions

For those who have been diagnosed with cancer or other diseases, being able to recognize an improvement in QOL, with improvement in "anxiety/depression" in particular is an affirmation of accepting reality and modifying one's behavior in a positive manner. It is apparent that Cancer Philosophy clinic has an important role in encouraging existing shift[10] positive manner.

Limitation

This survey was based on feedback from 28 out of 150 Cancer Philosophy Clinic, thus it is unclear whether the quality of all Cancer Philosophy Clinic has been assured or whether all clinics will show the same usefulness. In addition, in this study, only EQ-5D-5L was used to evaluate the clinical benefit.

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The authors declare that they have no conflict of interest.

Author contributions

MN and OH conceived the idea of the study. EI and OH developed the statistical analysis plan and conducted statistical analyses. OH supervised the conduct of this study. All authors reviewed the manuscript draft and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

Conflicts of interest statement

The authors declare that they have no conflict of interest.

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Publication List

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Publications from Juntendo University Graduate School of Medicine, 2020 [6/6]

Obstetrics and Gynecology

〈Original Articles〉

1) Saito M, Hirai C, Makino S, Takeda J, Nojiri S, Takeda S, Itakura A: A Restrospective Multicenter Study on the Usefulness of 50g Glucose Challenge Test in Gestational Diabetes Mellitus Screening. JMA J, 2020; 3: 125–130.
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編 集 後 記

COVID-19 が学術出版に及ぼした影響は甚大である。今回はこの影響を Journal Citation Reports（JCI）のデータから振り返ってみたい。はじめに JCI はクラリベートアナリティクスのデータベースであり、そのための偏りがあることはあらかじめご承知おきいただきたい。さて、まず見て取れるのは今回の未曾有の災害に対する世界の研究者たちの反応は極めて迅速かつ活発であったという点である。ウイルスの起源、拡散方式、病態理解について速やかに探究が行われ、わずか 2 年のうちに新しい治療法やワクチンの開発についての取り組みが行われたことは刮目に値し、それは Journal Impact Factor（JIF）のアップという形で反映されることになった。すなわち 2020 年にはみられなかった JIF100 超えのジャーナルが 2021 年には 7 誌登場し、そのいずれもが COVID-19 に関連する研究を大量に発表した雑誌であった。ちなみに 2021 年に最も引用が多かった 10 本の論文のうち 3 本を掲載した The Lancet の JIF は、前年の 79.3 から 250% 以上アップして 202.7 となり、New England Journal of Medicine（91.3 → 176.1）を抜いてランキング 1 位となった。また Nature は、1 年間に 100 万以上の総引用数を得た史上初のジャーナルという栄誉を獲得することとなった。ちなみに Nature において 500 以上の引用があった 16 項論文のうち 12 論文は COVID-19 に関連するものであった。しかしこのような論文の大量リリースは、同時にリサーチクオリティーの低下とジャーナルにおける引用の歪みという問題も引き起こしている。すなわち、研究においは最も重要である研究内容の信頼性が低下し、ジャーナルにおいては異常ともとれる自己引用数の増加が指摘されるようになっている。各ジャーナルの編集者はこの辺りに注意を払い、引き続き良質な論文の提供を心がけることが求められている。

射場敏明
救急・災害医学

イラスト作者より

成田山初詣の帰り道、不思議な骨董屋でおもしろいものを見つけました。ウサギの男の子が花束をさし出しながら女の子に恋の告白をしているところ。メルヘンチックな色合いに飛びつきました。卯年にピッタリのモチーフです。（宮道明子）

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抄　録

順天堂醫事雑誌
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当院における婦人科悪性腫瘍手術
～ ロボット支援下手術から他臓器合併切除手術まで ～

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女性生殖器の外陰，膣，子宮，卵管，卵巣のいずれにも悪性腫瘍を発症するが，特に子宮頸部や子宮体部，卵巣に多い．手術療法は婦人科がんの最も重要な治療法の１つである．当院では 2011 年から子宮体癌に対して先進医療として腹腔鏡下子宮体癌手術を開始し，保険収載に貢献した．我々が行ってきた腹腔鏡下子宮体癌手術をロボット支援下手術の da Vinci Xi システムを用いることで容易に，再現することができた．現在では，腹腔鏡下子宮体癌手術はすべてロボット支援下手術に切り替え，安全・確実に施行している．早期子宮頸癌に対する広汎子宮全摘術を，従来の開腹術と腹腔鏡下･ロボット支援下（低侵襲手術）の２群に分け，予後を比較した LACC trial の結果において，低侵襲手術は骨盤内再発が多く，開腹手術と比べて予後不良であった．子宮頸癌に対する低侵襲化の流れは世界的にも停滞している．卵巣がんは初期の段階では症状がほとんどないため，診断された時には腹腔内全体に癌が播種しているステージⅢ，Ⅳ期で見つかることが多い．卵巣癌では術後の残存腫瘍が予後と相関することから，手術は肉眼的残存腫瘍がない状態を目指した最大限の腫瘍減量手術を行う必要がある．そのため，播種・転移巣の可及的摘出のために腹膜切除術や腸管部分切除術などを必要とすることが多い．*BRCA1/2* 遺伝子の病的バリアント保持者に対する予防的卵管卵巣摘出術は卵巣・卵管癌発症予防のための重要な術式の１つである．子宮・卵巣は妊娠出産に必要な臓器であり，妊娠可能年齢の子宮，卵巣にがんができると妊娠できなくなることがある．妊娠できる可能性を残すことを考慮した手術をすることも重要である．手術やその後の治療が結婚や出産，性生活などにも影響することもりあり，癌の根治性を担保ししつ，患者さんには“女性”であることに向き合っていける治療法を提供することも重要である．

キーワード：婦人科がん手術，低侵襲手術，子宮体癌，子宮頸癌，卵巣癌

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抄　録

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最新の脳神経外科手術

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脳神経外科は，neuroscience や生理学，医療物理学にもとづいて手技が成り立っている．そのため，これらの分野で新しい発見や技術革新が起これば，それに付随して脳神経外科学も発展していくことになる．脳神経外科は発展し続ける学問である．

本稿では，2022 年現在の脳神経外科医療において，近年変革を遂げたと筆者が感じる分野につきその概略を示した．

頭蓋底外科分野では，経鼻内視鏡手術の応用範囲が広がりつつあり，脳腫瘍の診断は，分子生物学的性格から予後や腫瘍型が明確化された．中枢神経脳神経機能温存技術は，画像診断技術と機能評価技術が統合されることで格段の進歩を遂げ，さらにその技術は術前から手術中でも使用可能となってきている．

脳血管障害分野においては，血管内治療の発展が著しい．開頭術からカテーテル手術への以降のみならず，カテーテル手術で使用されるデバイスも変化してきている．脳動脈瘤治療においても，瘤内に複数のコイルを充填する治療から，特殊なステントをただ１つ留置する方法へ変わりつつある．さらに母血管の血流を整流化することで瘤内塞栓物質を用いずに瘤を退縮させる技術が本格運用されている．

こうした従来から対象としてきた疾患群に加え，近年では生活の質を向上させる外科手技に脳神経外科技術が用いられている．それらは，生命予後には直接的影響は少ないものの，社会復帰の難しい疾患群である．てんかんは，発作の管理が重要であり，薬物療法よりも外科介入が治療成績の優れた群が存在する．また，特発性正常圧水頭症による認知症治療では，脳脊髄液の管理を外科的に行うことで改善が得られる．従来，罹患したら社会復帰が難しい疾患群に脳神経外科的外科介入が行われることで社会復帰が実現しうるのである．

一方で，こうした疾患群であっても，外科的介入は不可逆的結果をもたらすことがある．したがって，その適応については普遍的な科学的根拠をもって判断されるべきである．

キーワード： 脳神経外科，開頭手術，経鼻内視鏡手術，機能外科

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抄　録

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頭頸部癌の最新治療
～ロボット手術，光免疫療法～

松　本　文　彦

順天堂大学医学部耳鼻咽喉科学講座

頭頸部外科学は頭頸部領域に発生する腫瘍を取り扱うが，この分野の近年の発展は目覚ましいものがある．早期に発見した癌を現在ではより低侵襲に切除を行う取り組みがなされており，ロボットを使用することにより従来であれば皮膚を切開する外切開が必要であった症例や放射線治療を行っていた症例をより低侵襲に短期間で治療することができる．実際の手術はカメラ１本と操作するロボットアームの２本，計３本を口から挿入し操作を行う．ロボットアームは先端が 360 度可動するため狭い口腔内でも細かな操作を行うことができる．また内視鏡は 3D 画像を提供し手術操作部位に近接することができるため小さな血管などを確認しながら手術をすすめることが可能である．課題としてはロボットアームに触覚がないため組織の硬さを感じることができないことや狭い口腔内に３本のアームが挿入されるためアーム同士が干渉しないように注意しながら操作する必要があることである．

光免疫療法は 2020 年の９月に条件付きで承認された新しい治療法である．まだ現在は既存の治療によっても再発もしくは転移をきたし，放射線，手術いずれの治療の適応もない症例が適応となる．治療の実際は処置前日に IR700 という色素を投与する．この色素は近赤外線を受けると細胞膜を破壊する特徴を有している．この色素を腫瘍特異的に届けるために腫瘍に比較的特異的に発現している EGFR 抗体に対する抗体薬を使用する．抗 EGFR 抗体に IR700 を結合した薬品（アキャルックス）を処置前日点滴にて投与する．処置当日は手術室で病変に近赤外線照射を全麻下に行う．近赤外線の照射法はフロンタルディフーザーとシリンドリカルディフーザーの２通りがある．本治療の抗腫瘍効果は高く腫瘍は比較的すみやかに縮小するが，問題点として近赤外線を照射する必要があるため病変が赤外線照射範囲内にあることが必須条件となる．また腫瘍が速やかに縮小するため治療後の組織欠損や腫瘍が頸動脈に浸潤している場合には腫瘍縮小による大出血の危険性があるため禁忌であることである．

キーワード： 頭頸部癌，ロボット手術，光免疫療法

この抄録は，順天堂醫事雑誌 69 巻 2 号，p97–102，2023 掲載の『The Latest Treatment for Head and Neck Cancers: Transoral Robotic Surgery and Photoimmunotherapy』の和文抄録です．

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順 天 堂 医 学 会
会長　服部　信孝

順天堂医学会短期海外留学時助成金給付制度

順天堂医学会では短期海外留学時助成金給付制度を開始いたしました。

1. 要件

下記すべての要件を満たす者

(1) 順天堂大学（大学院を含む）の学生で 1 か月以上 12 か月未満の海外留学をする者
(2) 留学先の研究機関または財団などからの援助がない者
(3) 医学会の正会員として 1 年以上の経歴を有し、医学会費を完納している者

2. 申請書類

(1) 順天堂医学会短期海外留学時助成金申込書
(2) 所属長の推薦書
(3) 申請者の主な研究テーマ・研究業績
(4) 留学受け入れ機関の指導者からの推薦状

3. 助成金の給付金額

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1 か月以上 4 か月未満	10 万円
4 か月以上 7 か月未満	20 万円
7 か月以上 12 か月未満	30 万円

4. 申請スケジュール（年 2 回）

申請期限	助成決定時期
6 月末	8 月
12 月末	2 月

5. 選考機関：順天堂医学会短期海外留学時助成金選考委員会

6. 助成後の義務

(1) 帰国後直近の順天堂医学会学術集会において研究成果の発表および、その内容を「順天堂醫事雑誌」に報告する。
(2) 帰国後は、順天堂大学またはその関連機関に原則として 3 年以上勤務する。

7. 本件の照会先

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