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Intraoperative consultation for ovarian tumors

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Introduction

Intraoperative frozen consultation is one of the most important and difficult tasks of pathologists. Frozen section (FS) is performed during surgery, from which the pathologist provides a preliminary diagnosis, hence guiding the surgeon in further management. The three main purposes of FS are to establish the presence and nature of a lesion, to determine the adequacy of the surgical margins, and to establish whether the obtained tissue contains diagnostic material or whether additional sampling is needed [1]. The indications and limitations of FS vary from organ to organ. However, this procedure should not be used by surgeons to satisfy their curiosity, to recognize normal anatomic structures, or to communicate immediately with the patient’s relatives. The pathologist responsible for the FS diagnosis requires experience, knowledge of clinical medicine and pathology, good judgment, and an awareness of the limitation of the FS method. To effectively obtain the result, the pathologist should review the patient’s clinical history and ideally have a discussion with the surgeon before the operation.

When the fresh tissue is received, the pathologist should select the best area from the specimen according to the purpose of the FS. The tissue is quickly frozen using liquid nitrogen, sectioned with cryostat, stained with hematoxylin-eosin, and evaluated under the microscope by the pathologist. Special stains and immunostains as well as cytologic smears obtained through touch preparation can be added [2]. Compared with routine pathologic diagnosis of formalin-fixed paraffin-embedded tissue preparations, FS evaluation is limited by suboptimal tissue quality, frozen artifacts, time limitation, and lack of ancillary studies. It is also affected by the pathologist’s experience, supportive persons, availability of a subspecialty pathologist, concurrent multiple FS specimens, and technical problems such as issues related to the instruments or the skill of the technician [3].

Gynecologic tumors are one of the most frequently encountered FS specimens in pathology laboratories. However, the evaluation of these lesions is often difficult because of the numerous disease entities and morphologic diversities, as well as their variants. Especially, ovarian tumors are a heterogeneous group of tumors including primary surface epithelial tumors, germ cell tumors and sex cord-stromal tumors, secondary tumors, and other groups of tumors of uncertain histogenesis or nonspecific stroma. Intraoperative FS is a very important and reliable tool that guides the surgical management of ovarian tumors. In this review, the diagnostic key points for the pathologist and the implication of the FS diagnosis on the operator’s decisions are discussed.

Keywords: Frozen section; Intraoperative consultation; Ovarian tumors
cord-stromal tumors, secondary tumors, and other groups of tumors of uncertain histogenesis or nonspecific stroma [4].

Helpful information for the FS diagnosis of an ovarian tumor includes the patient’s age; relevant clinical and familial history; history of malignancy; serum markers such as alpha-fetoprotein, carcinoembryonic antigen, carcinoma antigen 125, carbohydrate antigen 19.9, and human chorionic gonadotropin; hormone levels (estrogen, androgen); and imaging studies. A high concordance between FS diagnosis and final permanent section diagnosis has been reported, and the overall accuracy of FS diagnosis ranges between 80.7% and 97.1% for primary ovarian tumors [5,6]. However, the ultimate aim of FS in ovarian lesions is providing the surgeon with helpful information for the next step of the operation, rather than providing a specific pathologic diagnosis. If the tumor is benign, no further surgery is indicated. In borderline tumors, total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) and staging procedure are indicated in postmenopausal women; however, unilateral salpingo-oophorectomy (SO) and staging operation are indicated in young patients. In patients with ovarian carcinoma, TAH-BSO and debulking with staging procedure are recommended, whereas young patients with malignant sex cord-stromal tumors and germ cell tumors are suggested to undergo unilateral SO and staging procedure. Intraoperative FS is very important for guiding the surgical management of ovarian tumors.

In this review, the clinicopathologic, gross, and microscopic features of ovarian tumors are discussed, with special emphasis on the diagnostic key points and the implication of the FS diagnosis on the operator’s decision during surgery. The materials and data collected from four university hospitals (Korea Anam, Inje Busan Paik, Gyeongsang, and Dankook Cheil) between 2016 and 2017 were reviewed, and the classification of ovarian tumors followed the 2014 World Health Organization classification of tumors of the female reproductive organs [4].

**General categories of ovarian tumors**

A total of 491 cases were submitted for frozen diagnosis of ovarian tumors. Excluding nonneoplastic and nonovarian lesions, 446 tumors were primary ovarian tumors (95.5%) and 21 tumors were metastatic (4.5%) on permanent diagnosis. Among the primary tumors, 372 were surface epithelial tumors (83.4%), 43 were sex cord-stromal tumors (9.6%), and the remaining 31 were germ cell tumors (7.0%).

Surface epithelial tumors were classified into 166 mucinous tumors (44.6%), 120 serous tumors (32.3%), 43 endometrioid tumors (11.6%), 16 clear cell tumors (4.3%), 15 seromucinous tumors (4.0%), and 2 Brenner tumors (0.5%). The remaining 10 cases (2.7%) comprised 4 mixed carcinomas, 4 malignant mixed Mullerian carcinomas, 1 undifferentiated carcinoma, and 1 endometrial stromal sarcoma. Sex cord-stromal tumors were classified into 30 fibroma-thecoma tumors (69.8%) (19 fibromas, 6 cellular fibromas, 4 theciforms, and 1 thecoma), 11 granulosa cell tumors (GCTs) (25.6%), and 2 Sertoli-Leydig cell tumors (SLCTs) (4.6%). Germ cell tumors were classified into 23 mature cystic teratomas (74.2%), 3 dysgerminomas (9.7%), 2 immature teratomas (6.5%), 1 yolk sac tumor (3.2%), 1 choriocarcinoma (3.2%), and 1 mixed tumor (3.2%). The metastatic tumors comprised 17 adenocarcinomas, 2 malignant lymphomas, 1 squamous cell carcinoma, and 1 atypical carcinoid.

Thirty-six tumors reported as “benign” on FS were finally diagnosed as mucinous cystadenoma in 12 cases, endometriosis in 10 cases, serous cystadenoma in 9 cases, teratoma in 3 cases, mucinous borderline tumor (MBT) in 1 case, and seromucinous tumor in 1 case. Twenty-eight tumors reported as “adenocarcinoma” or “carcinoma” were finally diagnosed as serous carcinoma in 15 cases, endometrioid carcinoma (EC) in 4 cases, clear cell carcinoma in 2 cases, mucinous carcinoma in 2 cases, carcinosarcoma in 2 cases, and metastatic tumor in 2 cases.

**Surface epithelial tumors**

Tumors of surface epithelial origin are the most commonly encountered group in ovarian FS. Intraoperative FS evaluation is very important for determining the extent of surgery. In malignant tumors, staging laparotomy including total abdominal hysterectomy with bilateral SO, lymphadenectomy, peritoneal sampling, and omentectomy should be done, whereas limited cystectomy or unilateral SO is done for benign tumors, especially in young patients who want to preserve their fertility. Misinterpretation of FS may lead to unnecessary extensive surgery or a risk for a second operation. The distinction between borderline tumors and invasive cancers is sometimes difficult. A conservative approach may be appropriate, especially in young patients. The findings of careful gross examination, bilaterality, clinical history of a previous malignancy, and the patient’s age and reproductive status are important in intraoperative consultation. In addition, the differential diagnosis of surface epithelial tumors may include other primary ovarian neoplasms.

1. **Mucinous tumors**

Mucinous tumors are classified into benign cystadenoma/cystadenofibroma/adenofibroma, MBT/atypical proliferative mucinous tumor (APMT), and mucinous carcinoma. Mucinous tu-
Mucinous tumors are characterized by cyst and glands lined by epithelial cells containing intracytoplasmic mucin. They tend to be the largest of all ovarian tumors, with many of them being 15–30 cm in diameter and are typically unilateral. Approximately 75% are benign, 10% are borderline, and 15% are carcinomas. In the review of 166 frozen diagnosis of mucinous tumors, 67.5% were benign, 22.3% were borderline, and 10.2% were malignant.

1) Mucinous cystadenoma/cystadenofibroma/adenofibroma
Benign mucinous tumors are cystic, unilocular or multilocular, and contain viscous, mucoid material. If the tumor is partly or entirely solid, cystadenofibroma or adenofibroma is considered. The important point in intraoperative consultation is the distinction from other benign cysts, if possible, because a metastatic mucinous tumor from the appendix may sometimes mimic a primary benign mucinous cystic tumor. The surgeon may explore the appendix and perform appendectomy to exclude the possibility of an appendix origin. An additional FS or additional sampling for permanent section may be indicated in mucinous cystadenoma with focal epithelial proliferation and atypia.

Among 93 tumors diagnosed as mucinous cystadenoma on FS, 11 tumors were diagnosed as borderline, 8 as focally proliferative, and 2 as teratomas (1 mature and 1 immature) on permanent diagnosis. Twenty-two tumors diagnosed as cystadenoma with focal proliferation were diagnosed as borderline in 6 cases, cystadenoma in 4 cases, and seromucinous tumor in 1 case. Upgrading to a borderline tumor was seen in cases of cystadenoma (Fig. 1) and cystadenoma with focal proliferation. The distinction from a seromucinous tumor is not crucial on FS. Because mucinous ovarian tumors are commonly heterogeneous with a morphologic spectrum from benign to borderline to malignant areas, adequate sampling from the most solid area is very important for a correct diagnosis.

2) Mucinous borderline tumors/atypical proliferative mucinous tumors
Multilocular cystic tumors contain viscous mucoid material. A solid component is uncommon; however, if it is present, carcinoma or mural nodule should be considered. Because the tumor is heterogeneous in morphology, multiple areas should be sampled for FS. Epithelial proliferation is seen in > 10% of tumors, but no stromal invasion is noted.

MBT/APMT with intraepithelial carcinoma represents mucinous tumors showing areas of stratification to 4 or more layers or a cribriform pattern with severe nuclear atypia, but no stromal invasion. MBT/APMT with microinvasion indicates MBT with stromal invasion of < 5 mm.

Four tumors among 18 MBTs/APMTs and 2 of 4 MBTs/APMTs with microinvasion were diagnosed as mucinous carcinomas on permanent section (Fig. 2). Five of 6 tumors reported as MBTs/APMTs rather than mucinous carcinomas were finally diagnosed as mucinous carcinomas.

A definite diagnosis of intraepithelial carcinoma or microinvasion, and the distinction from seromucinous borderline tumor (SMBT) are not necessary in FS. The frozen diagnosis of MBT/APMT is adequate. If the distinction from a mucinous carcinoma

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**Fig. 1.** On frozen section, the multilocular cyst is lined by single layer of tall columnar cells (A), but the epithelial cells are stratified and show papillary growth indicating mucinous borderline tumor on permanent section (B).
is difficult, a frozen diagnosis of “at least MBT” can be made. Because of the excellent prognosis, even with intraepithelial carcinoma or microinvasion, fertility-sparing surgery is adequate for young patients with MBT/APMT [7].

3) Mucinous carcinomas
Mucinous carcinoma is a relatively rare histologic subtype and presents with a large, unilateral mass (> 10 cm). The tumor is complex and multicystic with solid areas. Necrosis and hemorrhage may be present. Two patterns of stromal invasion (> 5 mm), expansile (confluent) and destructive (infiltrative), should be identified (Fig. 3). The tumor may have areas resembling a benign cystadenoma or a borderline tumor (Fig. 4). Multiple adequate samplings from solid areas and areas near necrosis are key for the intraoperative FS diagnosis of MBT/APMT and mucinous carcinoma, because of the heterogeneous morphologic continuum from benign to borderline to malignant areas.

Among 7 tumors that were diagnosed as mucinous carcinoma on FS, 1 tumor was a clear cell carcinoma and 1 tumor was a metastatic carcinoma. The distinction from metastatic carcinoma is very important, because surgical staging should be done for a primary ovarian tumor but not for a metastatic carcinoma. Bilaterality, small tumor size (< 10 cm), and the patient’s clinical history of a prior malignancy indicate a metastatic carcinoma rather than a primary tumor [8]. The presence of a teratomatous component suggests a primary ovarian tumor.

Fig. 2. On frozen section, the tumor was diagnosed as mucinous borderline tumor (A), but permanent histologic section shows expansile type of mucinous carcinoma (B).

Fig. 3. Two patterns of invasion in mucinous carcinoma: expansile (A) and infiltrative (B).
4) Mucinous tumors with mural nodules
Reactive sarcoma-like mural nodules and malignant mural nodules are rarely associated with benign, borderline, or malignant mucinous tumors. A reactive mural nodule typically occurs in younger patients and does not alter the prognosis, whereas a malignant mural nodule characterized by anaplastic carcinoma or sarcoma is usually seen in older patients and has a poor prognosis (Fig. 5) [9,10]. High-grade carcinoma/sarcoma associated with a mucinous tumor may be enough for frozen diagnosis, and the final diagnosis can be deferred for permanent sections.

2. Serous tumors
Serous tumors are classified as benign cystadenoma/cystadenofibroma/adenofibroma, serous borderline tumor (SBT)/atypical proliferative serous tumor (APST), SBT/APST micropapillary variant/noninvasive low-grade serous carcinoma (LGSC),

Fig. 4. Goss finding of mucinous carcinoma is cystic, with polypoid mass (A). On section, the solid mass is sponge-like with hemorrhage and necrosis (B). The cystic area is mucinous borderline tumor (C), but solid portion is mucinous carcinoma (D).

Fig. 5. Mucinous borderline tumor shows mural nodule composed of anaplastic carcinoma.
invasive LGSC, and high-grade serous carcinoma (HGSC). Approximately 70% of serous tumors are benign, 10% are borderline, and 20% are carcinomas. However, among 120 serous tumors on FS, borderline and malignant tumors accounted for 22.5% and 43.3%, respectively, and benign tumors comprised only 24.2%.

1) Serous cystadenoma/cystadenofibroma/adenofibroma
Benign serous tumors usually occur in adults, and bilaterality is observed in about 20%. The tumor is a unilocular or an oligolocular cyst containing clear watery fluid. In cystadenofibroma, the tumor is cystic and solid and shows firm papillary projection, whereas the tumor is solid and firm with small spaces in adenofibroma. Epithelial proliferation involves < 10% of the epithelial lining [11]. If the frozen diagnosis is cystadenoma with focal epithelial proliferation, additional frozen sampling is recommended; however, no staging is required. The distinction from benign, nonneoplastic cyst is not important, but mucinous tumor should be ruled out because appendectomy may be done to exclude metastasis from a primary appendix tumor.

Among 22 benign serous tumors on frozen diagnosis, 1 tumor was borderline and 2 tumors were mucinous tumors. Among 4 benign versus borderline tumors, 1 was benign and the other was SMBT.

The distinction from a mucinous tumor should be based on the histologic cell type, not on the cystic content. The papillary projection in benign tumors is typically firm and small in number, whereas papillary growth in SBT/APST is soft, friable, and large in number.

2) Serous borderline tumor/atypical proliferative serous tumor
SBT/APST is bilateral in up to 55% of cases, and typically cystic. Abundant friable papillary projections are present on the inner lining of the cyst and/or a cauliflower-like mass may be present on the ovarian surface without a cystic component (serous surface papillary borderline tumor). Microscopically, epithelial proliferation is seen in at least 10% of tumors (Fig. 6). A micropapillary or cribriform pattern may also be seen ( < 5 mm). Psammomatous calcification, which may be observed in benign and malignant serous tumors, is found in approximately one-fourth of the cases. Microinvasion ( < 5 mm in greatest dimension) may be present. The distinction from serous cystadenoma with or without focal epithelial proliferation ( < 10%) is sometimes difficult on FS. A conservative approach is recommended, especially in young patients. If the stromal invasion is > 5 mm, it should be classified as invasive LGSC. If the micropapillary pattern is > 5 mm, it should be classified as noninvasive LGSC, micropapillary variant [11,12]. However, the distinction from noninvasive or invasive low-grade carcinoma is not crucial at the time of FS. “At least SBT” or “SBT with micropapillary features” is an appropriate FS diagnosis. HGSC requiring complete surgical staging should be ruled out on FS.

SBT/APST is associated with peritoneal implants in about 30–40% of the cases. The implants are classified into the noninvasive and invasive types, and the noninvasive type is subdivided into the epithelial and desmoplastic subtypes [13]. Invasive implants behave like LGSC [4]. The distinction between noninvasive implants of SBT/APST and LGSC may not be crucial at the time of FS, especially in older patients. Additional sampling from

Fig. 6. Serous borderline tumor on frozen section (A) and on permanent section (B). Epithelial proliferation is characterized by hierarchical branching papillae with budding and tufting, and stratification of the cells.
the peritoneum or ovary may be helpful for a specific diagnosis. Among 17 SBTs/APTs on FS, 1 tumor was SMBT. Among 6 borderline versus malignant tumors, 3 tumors were malignant and 1 was SMBT. The distinction from SMBT has no impact on the surgical management at the time of FS.

3) Noninvasive low-grade serous carcinoma
The clinical and gross findings of noninvasive LGSC (SBT/APT micropapillary variant) are similar to those of SBT/APST.

Microscopically, it is characterized by a nonhierarchical branching micropapillary or cribriform architecture in at least 1 confluent area measuring 5 mm [6]. Micropapillae are defined as at least 5 times taller than wide, with scant or no fibrovascular cores. The distinction from SBT/APST may not be crucial at the time of FS. "At least SBT" or "SBT with micropapillary features" may be enough for the frozen diagnosis, and fertility-sparing surgery may be done in young patients.

4) Low-grade serous carcinoma
LGSC is relatively rare and commonly advanced at the time of presentation. It is often bilateral and solid or partly cystic, with papillary growth. Microscopically, it is characterized by relatively uniform nuclei with mild to moderate atypia, and mitotic figures < 12/10 high-power fields (HPFs) [14]. Psammoma bodies may be abundant. Destructive stromal invasion (> 5 mm) is present. The distinction from SBT/APST may not be crucial at the time of FS. Additional biopsy from extraovarian lesions or implants may be helpful in identifying destructive stromal invasion. The value of fertility-sparing surgery is not well documented in this group, and the prognosis is dependent on the disease stage.

Pelvic or para-aortic lymph nodes are not infrequently involved by the papillary or glandular structures, similar to primary ovarian SBT/APST or LGSC. The distinction between primary nodal proliferation and metastasis from the ovary may be difficult. However, both findings do not change the prognosis and do not influence the treatment. Occasionally, extensive lymph node involvement in patients with invasive peritoneal implants is associated with a poor prognosis.

The distinction from HGSC should be done on FS. High-grade carcinoma characterized by marked nuclear atypia, numerous mitotic figures, and necrosis is different from low-grade carcinoma [14]. Unfortunately, most of the cases were not adequately diagnosed as LGSC or HGSC in this review.

5) High-grade serous carcinoma
HGSC is the most common type of ovarian carcinoma. It occurs in older age groups, presents at an advanced stage, and is bilateral in the majority of the cases. Grossly, the tumor is solid or solid and cystic with frequent involvement of the ovarian surface. Hemorrhage and necrosis are common. Histologically, the tumor is characterized by an admixture of solid, complex glandular growth with slit-like spaces, cribriform, and papillary patterns (Fig. 7). Marked nuclear atypia with prominent nucleoli, pleomorphism, and numerous mitotic figures (> 12/10 HPFs) with atypical forms are present [14]. Stromal invasion is present. A tumor with an intracystic papillary pattern showing marked nuclear atypia and numerous mitotic figures, but without stromal invasion, is also classified as HGSC. The important issue in FS is the recognition of high-grade epithelial malignancy. The distinction from LGSC is the presence of marked nuclear atypia and numerous mitotic figures (> 12/10 HPFs). The differential diagnosis from other high-grade carcinomas of Mullerian origin, endometrioid, clear cell carcinoma, and malignant Brenner tumor is not important. "High-grade carcinoma, consistent with a Mullerian origin" may be adequate in difficult cases. HGSC may arise from the fallopian tube or peritoneum and metastasizes from endometrial serous carcinoma. The distinction from these primary sites is not crucial on FS.

3. Endometrioid tumors
Endometrioid tumors include benign endometriotic cyst and cystadenoma/adenofibroma, endometrioid borderline tumor (EBT)/atypical proliferative tumor (APET), and malignant carcinoma. In the review of 43 frozen diagnoses, endometriotic cysts accounted for 70%, malignant tumors accounted for 25%, and borderline tumors accounted for 5.0%.

1) Endometriotic cyst/cystadenoma/adenofibroma
Endometriotic cyst is a cystic form of endometriosis. Histologically, the cyst is lined by endometrial epithelium and underlying endometrial stroma, but cystadenoma/adenofibroma is lacking the endometrial stroma. The distinction from other benign lesions is not crucial on frozen diagnosis. Endometriosis with cytologic atypia or atypical hyperplasia should be managed conservatively. However, adequate sampling is important because it may be associated with borderline and malignant endometrioid, clear cell, and seromucinous tumors.

In the review of 20 benign endometriotic lesions, 1 case was associated with clear cell carcinoma and the other was a mucinous cystadenoma. Sampling from a polypoid or solid lesion of an endometriotic cyst is considered important.

2) Endometrioid borderline tumor/atypical proliferative tumor
EBT/APET is an uncommon tumor that is predominantly solid
but shows a focally cystic or sponge-like cut surface. Histologically, the tumor shows complex, crowded glandular structures in a fibromatous or intracystic pattern. Squamous metaplasia is common. Mild to moderate nuclear atypia, but without stromal invasion, is present. EBT/APET with intraepithelial carcinoma is defined as marked cytologic atypia but without stromal invasion, whereas EBT/APET with microinvasion is defined as confluent glandular growth or stromal invasion of < 5 mm dimension.

Complete surgical staging is the standard surgical management for EBT/APET, but fertility-sparing surgery may be an option for young patients because of their excellent prognosis. The presence of intraepithelial carcinoma or microinvasion does not change the surgical management, but adequate sampling is recommended to confirm unequivocal invasion [15,16]. EC may arise in the background of EBT/APET or endometriosis. Six endometrioid tumors were interpreted as borderline versus malignant on FS, and 3 of them were finally diagnosed as EC.

The distinction from other primary ovarian serous, clear cell, and seromucinous carcinomas is not crucial; however, mucinous differentiation should be ruled out because of the possibility of a metastatic carcinoma. Metastatic carcinoma from a primary colorectal and endocervical tumor may mimic EC. Squamous differentiation and an association with EBT/APET or endometriosis in the background are the most helpful features indicating a primary ovarian origin. The “garland” pattern with intraluminal dirty necrosis is the feature indicative of metastasis. Information on the patient’s history of prior malignancies or concurrent lesions should be obtained from the surgeon. Simultaneous ovarian and endometrial ECs are present in 15–20% of the cases [18]. Whether the ovarian tumor is a primary tumor or a metastasis from the endometrium is not important on frozen diagnosis. Among 9 ECs, only 1 case was correctly diagnosed on FS and the others were serous carcinoma (5 cases), seromucinous carcinoma (1 case), mixed MC and EC (1 case), and metastatic carcinoma (1 case).

4) Endometrioid carcinoma
ECs occur in older age groups, and bilaterality is observed in up to 17% of the cases [4]. The tumor is a solid or blood-filled cyst with intraluminal soft mass or polypoid nodule. Histologically, the tumor resembles endometrial EC. The stromal invasion should be > 5 mm. Squamous differentiation is often present, in up to 30–50% of the cases (Fig. 8) [17]. Adequate sampling from solid and necrotic areas is important to rule out EC in the case of EBT/APET.

The distinction from other primary ovarian serous, clear cell, and seromucinous carcinomas is not crucial; however, mucinous differentiation should be ruled out because of the possibility of a metastatic carcinoma. Metastatic carcinoma from a primary colorectal and endocervical tumor may mimic EC. Squamous differentiation and an association with EBT/APET or endometriosis in the background are the most helpful features indicating a primary ovarian origin. The “garland” pattern with intraluminal dirty necrosis is the feature indicative of metastasis. Information on the patient’s history of prior malignancies or concurrent lesions should be obtained from the surgeon. Simultaneous ovarian and endometrial ECs are present in 15–20% of the cases [18]. Whether the ovarian tumor is a primary tumor or a metastasis from the endometrium is not important on frozen diagnosis. Among 9 ECs, only 1 case was correctly diagnosed on FS and the others were serous carcinoma (5 cases), seromucinous carcinoma (1 case), mixed MC and EC (1 case), and metastatic carcinoma (1 case).

4. Clear cell tumors
Benign tumors are exceptionally rare, and borderline tumors account for < 1%. Most tumors are clear cell carcinomas. Clear cell tumors arise as a solid adenofibromatous or a cystic endometriotic type [19,20]. In the solid type, the cut surface is sponge-like with numerous small cysts (Fig. 9A). A benign tumor is microscopically characterized by benign-appearing glandular epithelium, whereas a borderline tumor shows atypical or malignant epithelium without invasion or microinvasion. A frankly invasive component ( > 5 mm in size) is present in a malignant tumor. A cystic tumor is unilocular or multilocular, with protruding polypoid masses in the lumens (Fig. 9B). The lining of the cyst rep-
**Fig. 8.** Endometrioid adenocarcinoma shows confluent, back-to-back glandular proliferation with loss of intervening stroma (A), and squamous component (B).

**Fig. 9.** Clear cell carcinoma may have a solid cut surface (A) or may show a predominantly cystic appearance with intraluminal solid growth (B). On frozen section, the tumor has solid and papillary growth patterns and psammomatous calcification (C). The tumor cells are large and pleomorphic. Hyaline bodies are found (D).
resents benign or atypical endometriosis. The tumors are characterized by various cell types and histologic patterns (Fig. 9C). The most diagnostic features include dense hyalinized cores of papillae and hyaline bodies, which are present in 25% of the cases (Fig. 9D). Because a benign or borderline clear cell tumor is exceedingly rare, multiple additional sections should be taken to rule out carcinoma. Marked nuclear atypia is helpful in the differentiation of intracystic papillary clear cell carcinoma from SBT/APST. The distinction from primary ovarian HGSC and EC as well as the distinction between metastatic clear cell carcinoma and Mullerian clear cell carcinoma are not crucial on FS. Yolk sac tumor and dysgerminoma should be ruled out, because fertility-sparing surgery is an option for young patients. Germ cell tumors typically occur in younger age groups (2nd and 3rd decades) than clear cell carcinoma. All 11 clear cell carcinomas diagnosed on FS were correct; however, 3 tumors were diagnosed as adenocarcinoma and 1 as mucinous carcinoma. The other 1 case arising in association with endometriosis was misdiagnosed as endometriosis.

5. Seromucinous tumors
Seromucinous tumor is a mixed epithelial neoplasm with 2 or more Mullerian cell types, all accounting for at least 10% of the epithelium. The tumors are unilocular or paucilocular with papillary excrescences (Fig. 10A). Seromucinous tumors are associated with endometriosis in 30% of the cases (Fig. 10B) [4]. The most predominant epithelial cell types are serous and endocervical-type mucinous epithelium (Fig. 10C). The tumors are classified into benign seromucinous cystadenoma/adenofibroma, borderline seromucinous tumor/atypical proliferative seromucini-

Fig. 10. Seromucinous borderline tumor is grossly cystic and shows intraluminal papillary growth (A). Histologically papillary growth is similar to serous borderline tumor (B). Frozen (C) and permanent (D) sections show complex glands composed of serous and mucin-secreting cells infiltrated with neutrophils.
tumors, and malignant seromucinous carcinoma. Benign and malignant tumors are rather uncommon, and most tumors belong to the borderline category. These tumors are architecturally similar to SBT/APST, but larger papillae have edematous stroma containing neutrophils (Fig. 10D). Microinvasion, intraepithelial carcinoma, and a micropapillary pattern may occur.

On FS, the distinction from SBT/APST may be difficult; however, it is not important at the time of FS.

Seromucinous tumors were frequently diagnosed as serous tumors, but also as mucinous or endometrioid tumors in this review.

**Sex cord-stromal tumors**

Sex cord-stromal tumors account for approximately 5–10% of all ovarian tumors and are commonly associated with estrogentic or androgenic manifestations. The tumors are classified into pure stromal tumors, pure sex cord tumors, and mixed sex cord-stromal tumors, and present a variety of histologic types [6]. Because the biologic behavior of sex cord-stromal tumors differs according to the histologic type, recognition of the specific entity may guide the intraoperative management.

1. **Fibroma-thecoma**

   Fibroma is the most common type of stromal tumor. The tumor is solid, firm, white or tan, or hemorrhagic because of torsion (Fig. 11A). Microscopically, the tumor is composed of intersecting bundles and fascicles of spindle cells with hyalinization, collagen bands, or plaque (Fig. 11B). Cellular fibroma accounts for about 10% and is densely cellular with scant collagen. The number of mitosis is \( \leq 3/10 \) HPFs, and nuclear atypia is absent or mild. A cellular tumor with mitotic activity of \( \geq 4/10 \) HPFs and no more than mild nuclear atypia is defined as mitotically active cellular fibroma, whereas a tumor with at least moderate nuclear atypia and increased mitotic activity of \( \geq 4/10 \) HPFs, often with atypical form, is termed as fibrosarcoma [21].

   Thecomas are relatively uncommon tumors that typically occur in postmenopausal women with symptoms of estrogen production. The tumors are unilateral, and the cut surface is solid and yellow. The tumor is microscopically composed of sheets of oval or round cells with moderate to abundant pale eosinophilic cytoplasm. The tumor is designated as a fibrothecoma when an area resembling a fibroma is present.

   On FS, the distinction of fibroma from thecoma is not important. However, the distinction from metastatic carcinoma with reactive stromal proliferation (Krukenberg tumor) is important. Bilaterality should raise a suspicion for metastasis, and careful microscopic examination to search for scattered tumor cells with a signet ring or breast lobular carcinoma should be done. Thorough sampling is recommended when minor sex cord elements are present, to rule out GCT or SLCT. Luteinized cells in thecomas may suggest the possibility of Leydig cell tumor or SLCT. Distinction from Leydig cell tumor is not crucial, but identification of a Sertoli cell component is important because surgical staging is required for SLCT [22].

   Among 30 tumors, 1 fibrothecoma was suggested to be a metastatic poorly differentiated carcinoma and 3 cellular fibromas were diagnosed on permanent section.

2. **Granulosa cell tumors**

   GCT is a low-grade malignant tumor composed of granulosa

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Fig. 11. Cut surface of fibroma is solid, firm, tan white and yellow (A). Histologically, the tumor is hypercellular and hypocellular with interlacing fascicles of spindle tumor cells (B).
cells often with a variable number of fibroblasts and theca cells. The tumors comprise of two different clinicopathologic subtypes: adult and juvenile. The adult type more often occurs in postmenopausal patients, whereas the juvenile type mainly occurs in children and younger women. The patients may present abnormal vaginal bleeding associated with estrogenic manifestations. Patients with adult GCT have concurrent endometrial hyperplasia (25%) or adenocarcinoma (5%), and younger patients may present isosexual precocity [23]. The tumors are commonly unilateral, typically solid and cystic, and tan-yellow or white. Microscopically, the adult form is characterized by a mixture of various morphologic patterns, and the tumor cells are uniform with scanty cytoplasm and pale grooved nuclei (Figs. 12A, 12B). The juvenile form typically shows macrofollicles filled with basophilic secretions, as well as cells with moderate to abundant cytoplasm and darker nuclei usually without grooves [24].

The surgical treatment of GCT in postmenopausal patients includes total hysterectomy and bilateral SO as part of the complete surgical staging procedure, whereas fertility-sparing surgery including unilateral SO and staging procedure may be done in younger patients with unilateral tumor without surface involvement [25,26]. On FS, the distinction between the adult and juvenile forms is not crucial. The distinction of the adult type from benign sex cord-stromal tumors and metastatic carcinoma is the most important, because these lesions do not require surgical staging. Clinical history, bilaterality, and marked nuclear atypia with numerous mitotic figures should raise suspicion for a metastatic carcinoma. An adult-type tumor with a microfollicular pattern can mimic a metastatic or primary typical or atypical carcinoid tumor. Carcinoid tumors have round nuclei with smooth nuclear membrane and stippled chromatin, in contrast to oval nuclei and nuclear groove in GCT (Figs. 12C, 12D). In the distinction of the sarcomatoid type from cellular fibroma/fibrosarcoma, the characteristic nuclear features and identification of other morphologic pat-
terns of GCT can be helpful. If the frozen diagnosis is adult GCT, evaluation of the endometrium is also recommended.

One SLCT and 1 metastatic atypical carcinoid were diagnosed as adult GCT on FS.

3. Sertoli-Leydig cell tumors

SLCT is a rare tumor that commonly occurs in young patients and presents androgenic symptoms. Most of the tumors are unilateral, solid, and tan-yellow, or partly cystic in tumors with a retiform pattern or a mucinous heterologous component. Microscopically, the tumor is characterized by open or solid tubules, cords and diffuse sheets of primitive stromal appearance of Sertoli cells, and a variable degree of Leydig cells (Fig. 13A). The tumors are classified into well, moderately, and poorly differentiated groups, according to the differentiation of Sertoli cells. Approximately 20% of the tumors have heterologous components such as mucinous epithelium, cartilage, or skeletal muscle, and approximately 15% of SLCTs show a retiform pattern [4,27]. The prognosis of patients depends on the differentiation and on the presence of retiform and heterologous components [28]. Conservative fertility-sparing surgery in young patients with stage 1 tumor includes unilateral SO and staging procedure; however, bilateral SO, total hysterectomy, and complete surgical staging are performed in patients who do not wish to preserve fertility [22].

The differential diagnosis between moderately and poorly differentiated SLCT and adult GCT is not easy on FS, but the surgical management is basically similar (Fig. 13B). In distinguishing from ovarian primary sertoliform EC, the presence of unilateral-ty, younger age, absence of squamous differentiation, and presence of Leydig cells can be helpful in the diagnosis of SLCT. Surgical staging is more extensive in ovarian epithelial malignancy. Among 2 SLCTs, 1 tumor was diagnosed as adult GCT on FS.

Germ cell tumors

Germ cell tumors comprise the second most common type of tumors; however, the majority of tumors are benign mature cystic teratomas. Malignant germ cell tumors are relatively rare, but the recognition of these tumors and their distinction from aggressive epithelial carcinomas are crucial. Because most malignant germ cell tumors occur in young patients, fertility-sparing surgery is important. Fortunately, adjuvant chemotherapy is now the standard management for these tumors. The patient’s age, hormonal manifestations such as precocious puberty, and serum tumor markers can provide the diagnostic clues for the FS diagnosis. Approximately 20% of the tumors have heterologous components such as mucinous epithelium, cartilage, or skeletal muscle, and approximately 15% of SLCTs show a retiform pattern [4,27]. The prognosis of patients depends on the differentiation and on the presence of retiform and heterologous components [28]. Conservative fertility-sparing surgery in young patients with stage 1 tumor includes unilateral SO and staging procedure; however, bilateral SO, total hysterectomy, and complete surgical staging are performed in patients who do not wish to preserve fertility [22].

The differential diagnosis between moderately and poorly differentiated SLCT and adult GCT is not easy on FS, but the surgical management is basically similar (Fig. 13B). In distinguishing from ovarian primary sertoliform EC, the presence of unilateral-

Fig. 13. Sertoli-Leydig cell tumor (A) has sex cord component similar to adult granulosa cell tumor (B), but Leydig cell component is present in Sertoli-Leydig cell tumor (circle in A).
ity is observed in 10–15% of the cases. Mature teratoma is almost always cystic, but rarely solid. Immature teratoma is solid and cystic. Microscopically, the neural elements in mature teratoma may mimic the primitive immature neuroepithelial tissue of immature teratoma [29]. Immature mesenchymal and endodermal elements are sometimes difficult to detect on FS. The diagnosis of immature teratoma should rely on the identification of immature neuroepithelial tissue (Fig. 14A). Carcinosarcoma, composed of carcinomatous and sarcomatous components, may be considered in the differential diagnosis, but it most often occurs in the postmenopausal ages (Fig. 14B). Monodermal teratomas include struma ovarii and carcinoid tumor. Malignant transformation of mature teratoma rarely occurs, most often in postmenopausal patients; however, when it occurs, full surgical staging is required [30]. The FS diagnosis of mature cystic teratoma is straightforward, but adequate sampling from solid areas including the Rokitansky protuberance should be done.

2. Dysgerminoma
Dysgerminoma is the most common malignant germ cell tumor, occurring most often during the 2nd and 3rd decades of life. It is a rapidly growing tumor and may arise in dysgenetic gonads with gonadoblastoma. The tumor is unilateral in 80–90% of the cases, and is large, solid, and flesh and tan-yellow in color (Fig. 15A). Microscopically, the tumor is characterized by solid nests, sheets, or cords of relatively uniform polygonal cells with abundant clear or eosinophilic cytoplasm and prominent nucleoli, with intersecting fibrous septae infiltrated with lymphocytes (Fig. 15B).

On FS, contralateral ovarian biopsy should be performed to rule out bilateral tumor or underlying dysgenetic gonads and/or gonadoblastoma, for which bilateral oophorectomy is indicated. However, fertility-sparing surgery (unilateral SO with peritoneal biopsy and lymph node sampling) is adequate for unilateral dysgerminoma [31]. The distinction from other malignant germ cell tumors, yolk sac tumor and embryonal carcinoma is not crucial on FS. The surgical management is essentially identical. The most important issue concerning dysgerminoma on FS is its differentiation from diffuse large cell lymphoma, because the management of lymphoma is basically nonsurgical (Figs. 15C, 15D). One of 2 dysgerminomas was diagnosed as metastatic carcinoma, whereas 1 malignant lymphoma was interpreted as dysgerminoma on FS in this review.

3. Yolk sac tumor
Yolk sac tumor accounts for 20% of malignant germ cell tumors and occurs during the 2nd and 3rd decades of life. This tumor may be a component of a mixed germ cell tumor and rarely occurs in association with a surface epithelial tumor, usually endometrioid [32, 33]. The serum alpha-fetoprotein level is elevated. The tumor is nearly always unilateral, large, solid, and tan-yellow, with areas of necrosis, hemorrhage, and cyst formation. Microscopically, various growth patterns, such as reticular pattern, endodermal sinus pattern with Schiller-Duval bodies, solid pattern, alveolar glandular pattern, and other rare polyvesicular vitelline or hepatoid patterns, are present within the same tumor (Fig. 16).

The distinction from other malignant germ cell tumors is not crucial on FS, because the surgical management is similar. The most important entity in the differential diagnosis is clear cell

Fig. 14. Immature teratoma shows primitive neuroepithelial component, in addition to immature epithelial and mesenchymal tissues including immature cartilage (A), whereas carcinosarcoma is composed of carcinomatous (B, left) and sarcomatous components with malignant-looking cartilage (B, right).
Fig. 15. Dysgerminoma shows pale gray, solid, and lobulated cut surface (A), and histologically is characterized by sheets of large polygonal cells separated by fibrous septa with infiltration of lymphocytes on frozen section (B). Malignant lymphoma shows homogeneous, fish flesh cut surface (C), and diffuse infiltration of large lymphoid cells (D).

Fig. 16. Yolk sac tumor shows reticular, alveolar and papillary growth patterns (A). The tumor cells are large, pleomorphic and contain hyaline globules (B).
carcinoma, which requires more extensive staging. Clear cell carcinoma usually occurs in older ages and is commonly associated with endometriosis.

4. Choriocarcinoma
Choriocarcinoma is a rare type of malignant germ cell tumor. Nongestational choriocarcinoma occurs in children and young adults and may be mixed with other malignant germ cell tumor components, whereas gestational choriocarcinoma occurs in older age groups. Elevated serum beta-human chorionic gonadotropin level and isosexual pseudoprecocity may be present. The tumor is typically large and solid and cystic, often with hemorrhage and necrosis. Microscopically, a biphasic pattern of cytotrophoblasts and multinucleated syncytiotrophoblasts is typically present (Fig. 17). Other malignant germ cell tumors may show isolated syncytiotrophoblastic giant cells, but the distinction on FS is not crucial. However, poorly differentiated surface epithelial carcinoma with trophoblastic differentiation, typically occurring in postmenopausal patients, should be differentiated because it requires more aggressive surgery [34]. One choriocarcinoma in this review was interpreted as torsion because of the presence of extensive hemorrhagic necrosis.

Metastatic tumors
Metastatic tumors account for about 15% of ovarian malignancies and 6–7% of all adnexal masses [35]. Among 467 cases of ovarian tumors, 21 (4.5%) cases were metastatic tumors. Ovarian metastasis most commonly originates from the gastrointestinal tract (colon, appendix, stomach, and pancreatobiliary tract). The breast is the most frequent primary site among the nongastrointestinal origins [36]. Endometrial and cervical carcinoma may metastasize to the ovary. Metastatic ovarian tumor can be present synchronously or metachronously with the primary neoplasm, but an ovarian tumor may represent the first manifestation of an occult nonovarian primary neoplasm. Metastatic tumors are bilateral in approximately 70% of the cases, are small in size (< 10 cm), and show superficial surface involvement and multinodular growth; however, they can be unilateral, large, and cystic, resembling a primary ovarian neoplasm [37]. Microscopically, metastatic tumors are characterized by surface implants, multinodularity, lymphovascular invasion, and extensive extraovarian spread. However, the microscopic appearance of the metastasis is variable depending on the primary tumor, although the histologic features of metastatic tumors are not always identical to those of the primary tumors.

Among 19 metastatic tumors excluding 2 malignant lymphomas, 17 tumors were adenocarcinomas, 1 tumor was a squamous cell carcinoma, and 1 was an atypical carcinoid. The primary sites were the stomach in 8 cases, the colon in 4 cases, the uterine cervix in 3 cases, and unknown in 3 cases. The 3 tumors among 19 metastatic tumors were misinterpreted as 1 mucinous carcinoma, 1 EC, and 1 GCT.

1. Colorectal adenocarcinoma
Metastatic adenocarcinoma from the colorectum is often bilateral and solid or solid and cystic with a tan-yellow or gray cut surface (Fig. 18A). Ovarian surface involvement and multinodular growth pattern are commonly seen. Histologically, the tumor shows variable-sized, often cystic, irregular glands. A cribriform pattern...
architecture with dirty necrosis is called a garland pattern. The differential diagnosis from primary ovarian mucinous and endometrioid adenocarcinoma is important (Fig. 18B). Bilaterality, size < 10 cm, ovarian surface involvement, and a multinodular growth pattern suggest metastasis rather than a primary ovarian tumor [37]. If the tumor shows mucinous differentiation, intraoperative surgical evaluation of the abdominal cavity is recommended to find the possible primary lesion of the metastasis. Squamous differentiation in adenocarcinoma indicates primary ovarian EC rather than metastasis from a primary colorectal tumor.

2. Signet ring cell carcinoma
The primary site of metastatic signet ring cell carcinoma is most commonly the stomach (70%), but less commonly the colorectum, appendix, breast, and pancreaticobiliary system [38,39]. The tumor is bilateral, grossly solid, and tan-yellow or white, but may also be firm or soft, and gelatinous (Fig. 19A). Histologically, the tumor shows a pseudo-lobular pattern with hypercellular and hypocellular areas or diffusely cellular dense stroma (Fig. 19B). Signet ring cells individually infiltrate or form small clusters or tubules. Extracellular mucin may be present. On FS, signet ring cells may be missed and misinterpreted as fibroma or fibrothecoma. Primary ovarian sex cord-stromal tumors are usually unilateral.

3. Appendiceal tumors
The most common appendiceal tumor with ovarian involvement is low-grade mucinous neoplasm. Less commonly, intestinal-type

![Fig. 18. Multilocular cystic metastasis from colon cancer with multifocal yellow necrotic foci (A). Garland pattern with central necrosis simulates endometrioid carcinoma on frozen section (B).](https://doi.org/10.12701/yujm.2019.00227)

![Fig. 19. Metastatic signet ring cell carcinoma involving both ovaries (A). Fibrous stroma is infiltrated with nests and cords of small tumor cells on frozen section (B).](https://doi.org/10.12701/yujm.2019.00227)
adenocarcinoma, signet ring cell carcinoma, and goblet cell carcinoid tumor may involve the ovary. Low-grade mucinous neoplasm is often associated with pseudomyxoma peritonei and is frequently bilateral, but shows predominantly right-sided involvement among unilateral cases [40]. The cut surface reveals a multilocular cyst with tan-gray, mucoid appearance and surface involvement. The appendix is dilated with mucus. Histologically, the cysts are lined by flat or undulating mucinous epithelium with spillage of mucin into the stroma (pseudomyxoma ovarii). Goblet cells may be present. The mitotic activity is not significant. The presence of pseudomyxoma peritonei, bilaterality, and ovarian surface involvement indicate appendiceal metastasis rather than primary ovarian tumor [41]. However, similar morphologic features may be present in a primary mucinous tumor associated with a mature teratoma (Fig. 20). Appendectomy and FS evaluation of the appendix should be done even in the absence of gross abnormalities.

4. Uterine cervical and endometrial carcinomas
Uterine cervical adenocarcinoma and, less commonly, squamous cell carcinoma may spread to the ovary, even in cases in which the primary tumor is small and clinically unsuspected for ovarian metastasis. Histologically, the tumors may mimic primary borderline or malignant mucinous and endometrioid tumors [42]. Endometrial and ovarian involvement by endometrioid or serous carcinoma may represent a synchronous independent primary tumor or ovarian metastasis from a primary endometrial tumor. The distinction between these possibilities is impossible at the time of FS and is usually not crucial for the intraoperative surgical management.
Conclusion

The discrepancies between frozen diagnosis and permanent diagnosis are mainly due to sampling errors and misinterpretation by pathologists but may also be due to suboptimal quality of the FS. If the diagnosis is doubtful, the gross specimen should be re-examined and additional sections should be taken, a second opinion from an experienced pathologist should be obtained, and promptly discuss with the surgeon to obtain more history information and to discuss about a difficult diagnostic interpretation.

Conflicts of interest

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

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References


Cognitive dysfunctions in individuals with diabetes mellitus

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Some patients with type 1 and type 2 diabetes mellitus (DM) present with cognitive dysfunctions. The pathophysiology underlying this complication is not well understood. Type 1 DM has been associated with a decrease in the speed of information processing, psychomotor efficiency, attention, mental flexibility, and visual perception. Longitudinal epidemiological studies of type 1 DM have indicated that chronic hyperglycemia and microvascular disease, rather than repeated severe hypoglycemia, are associated with the pathogenesis of DM-related cognitive dysfunction. However, severe hypoglycemic episodes may contribute to cognitive dysfunction in high-risk patients with DM. Type 2 DM has been associated with memory deficits, decreased psychomotor speed, and reduced frontal lobe/executive function. In type 2 DM, chronic hyperglycemia, long duration of DM, presence of vascular risk factors (e.g., hypertension and obesity), and microvascular and macrovascular complications are associated with the increased risk of developing cognitive dysfunction. The pathophysiology of cognitive dysfunction in individuals with DM include the following: (1) role of hyperglycemia, (2) role of vascular disease, (3) role of hypoglycemia, and (4) role of insulin resistance and amyloid. Recently, some investigators have proposed that type 3 DM is correlated to sporadic Alzheimer’s disease. The molecular and biochemical consequences of insulin and insulin-like growth factor resistance in the brain compromise neuronal survival, energy production, gene expression, plasticity, and white matter integrity. If patients claim that their performance is worsening or if they ask about the effects of DM on functioning, screening and assessment are recommended.

Keywords: Alzheimer’s disease; Cognition; Dementia; Diabetes

Introduction

Diabetes mellitus (DM) is a metabolic disease that can cause complications in the peripheral nervous system and several organs in the body, including the kidney, eyes, and brain [1]. Among the complications of DM, cognitive dysfunctions are relatively less addressed. Some patients with type 1 and 2 DM present with cognitive dysfunctions. Both hypoglycemia and hyperglycemia are known to cause cognitive dysfunctions. However, the underlying pathophysiology is not well understood [2]. Research results about one hypothesis are conflicting, and studies with consistent results are not available. In addition, the most appropriate method for diagnosing, treating, and preventing cognitive dysfunctions in DM is not yet identified [2]. Although the mechanisms and results remain inconsistent, some patients with DM present with cognitive dysfunctions, and the decline in cognitive function has a significant impact on activities of daily living. Therefore, cognitive dysfunctions in patients with DM must be reviewed and summarized to obtain useful information. The
present study aimed to review the characteristics of cognitive dysfunctions in patients with DM to summarize the factors affecting cognitive functions and the hypotheses about the mechanisms of cognitive dysfunctions.

Cognitive dysfunctions in type 1 diabetes mellitus

In a recent meta-analysis [3] that included 33 studies, the authors have analyzed the result of the cognitive function assessment performed during normal blood glucose state in adults with type 1 DM. Results showed that some cognitive domains, including speed of information processing, psychomotor efficiency, visual and sustained attention, mental flexibility, and visual perception, were significantly impaired in patients with type 1 DM compared with those of the controls. However, the cognitive domains of patients with type 1 DM were not significantly different from those of the controls, which include memory, motor speed, selective attention, and language. A recent systematic review [2] has shown that cognitive dysfunctions commonly observed in patients with type 1 DM are associated with the decreased speed of information processing, psychomotor efficiency, attention, memory, learning, problem solving skills, motor speed, vocabulary, visuoconstruction, visual perception, somatosensory examination, motor strength, mental flexibility, and executive function. Among these areas, decreased speed of information processing, psychomotor efficiency, attention, visuoconstruction, and mental flexibility have strong supporting data (Table 1).

In the early 1990s, cognitive dysfunctions in type 1 DM were more prominent in individuals who repeatedly presented with severe hypoglycemia. This finding is consistent with those of anecdotal reports of severe hypoglycemia that leads to cortical changes in the frontal lobe and in other regions of the brain, such as the temporal lobe, basal ganglia, and hippocampus [4,5]. However, a more recent evidence indicated that hypoglycemic episodes may not cause cognitive dysfunctions. The results of longitudinal epidemiological studies have indicated that chronic hyperglycemia and microvascular complications cause DM-related cognitive dysfunctions. The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications is a 18.5-year longitudinal epidemiological study with 1,144 participants. Of these participants, 40% had experienced one or more severe hypoglycemic episodes (blood glucose concentration < 2.8 mmol/L accompanied by seizure or coma) during the study period. However, hypoglycemic episodes and cognitive dysfunctions were not significantly associated [6]. Rather, the 5 independent variables predicting the decrease in psychomotor speed over a follow-up period of 18.5 years were as follows: old age, low education, high lifetime hemoglobin A1c (HbA1c) concentrations, proliferative diabetic retinopathy, and renal complications [7]. In addition, an increase in carotid intima-media thickness was slightly associated with a decline in cognitive performance. In particular, retinopathy was most closely associated with cognitive dysfunctions in this study [6]. A limitation of this study is that only younger participants (aged < 50 years) were included; thus, the study might have been conducted before the onset of cognitive dysfunctions due to hypoglycemia. However, this study showed that the risk of cognitive dysfunctions is lower, and the progression is also slower in young patients with DM who have good glycemic control. Systematic meta-analyses with similar results have reported that repeated hypoglycemia and cognitive decline were not correlated [3]. Several other studies have reported that microvascular complications are associated with an increased risk of cognitive decline [8].

However, hypoglycemia is associated with decreased cognitive function in the high-risk group, which was diagnosed early within the first few years of life [9,10]. Moreover, diagnosis at a younger age in patients with type 1 DM is associated with an increased risk of cognitive dysfunctions. Those who developed type 1 DM before the age of 4 years had impaired executive skills, attention, and processing speed compared to those diagnosed after the age of 4 years [11].

Appropriate glycemic control plays an important role in the cognitive functions of patients with type 1 DM. Better glycemic control improves functions, such as psychomotor efficiency, attention, motor speed, memory, and academic achievement [2]. In a DCCT study, patients with type 1 DM with a mean glycated hemoglobin (HbA1c) of 7.4% had significantly better motor speed and psychomotor efficiency than those with a mean HbA1c of 8.8% [6].

Cognitive function was worse in patients with type 1 DM who presented with DM complications. One study has reported that deficits in fluid intelligence, information processing, attention, and concentration are correlated to the presence of background

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**Table 1.** Cognitive dysfunction domains frequently reported by diabetes mellitus types

<table>
<thead>
<tr>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
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<tbody>
<tr>
<td>Speed of information processing</td>
<td>Memory</td>
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<tr>
<td>Psychomotor efficiency</td>
<td>Psychomotor speed</td>
</tr>
<tr>
<td>Attention</td>
<td>Frontal lobe/executive function</td>
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<tr>
<td>Mental flexibility</td>
<td></td>
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<td>Visual perception</td>
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DM, diabetes mellitus.
retinopathy [12]. Periods of DM, proliferative retinopathy, macrovascular complications, and hypertension have been associated with decreased performance in psychomotor speed and visuoconstruction ability tests in patients with type 1 DM [13-15] (Fig. 1).

Several studies have reported that gender in patients with type 1 DM is associated with cognitive function. Skenazy and Bigler [16] have indicated that men with type 1 DM had decreased performance in measuring oscillation, strength grip, and somatosensory function than male controls, and the magnitude of this difference was greater than that between women with type 1 DM and gender-matched controls. A decline in verbal intelligence was observed in boys aged between 7 and 16 years with type 1 DM and was correlated with a deterioration in glycemic control. This was not observed in girls of the same age [17]. However, several studies have not observed gender differences. Future research with a better study design must be conducted.

**Cognitive dysfunctions in type 2 diabetes mellitus**

Numerous reports have shown that patients with type 2 DM are at increased risk of Alzheimer’s disease (AD) dementia and vascular dementia [18-22]. According to Bruce et al. [23], 17.5% of elderly patients with type 2 DM present with moderate to severe deficits in activities of daily living; 11.3% with cognitive impairment; and 14.2% with depression. A recent systematic review [2] has shown that cognitive dysfunctions commonly reported in patients with type 2 DM are associated with memory, psychomotor speed, executive function, processing speed, complex motor function, verbal fluency, and attention. Among these areas, memory, psychomotor speed, and executive function have strong supporting data (Table 1). By contrast, in some studies, the effects of subtle neurocognitive impairment on the daily activities of patients with type 2 DM are not fully elucidated, and there is a debate on whether such condition is attributed to changes in diabetic brain function [24]. In particular, the problem in daily function observed in patients with type 2 DM may be due to depression [23].

Proper glycemic control plays an important role in the cognitive function of patients with type 2 DM. In nearly 2,000 postmenopausal women, those with an HbA1c ≥ 7.0% had a fourfold increased risk of developing mild cognitive impairment [25]. Grodstein et al. [26] have found that elderly participants who were receiving oral diabetic medications, other than insulin, had similar cognitive scores with participants without DM. Other studies have shown an inverse relationship between HbA1c and working memory [27,28], executive function [27], learning [29], and complex psychomotor performance [29,30] in patients with type 2 DM, thereby supporting the hypothesis that worsening glycemic control leads to cognitive dysfunctions similar to those observed in type 1 DM.

Nevertheless, the benefits of aggressive glucose management in type 2 DM are not fully elucidated [31-33]. The target value of HbA1c in intensive therapy in the study was approximately < 6.0% or > 1.5% lower than that in the standard therapy (targeting level of 7.0–7.9%). However, several studies have shown that intensive glycemic control did not have a positive effect on cognitive function [31-34]. The Memory in Diabetes substudy of the Action to
Control Cardiovascular Risk in Diabetes trial has reported that aggressive glucose-lowering therapy did not have positive effects on not only cognitive function but also total brain volume during the 40-month follow-up in patients with type 2 DM [34].

Similar to type 1 DM, type 2 DM is associated with deficits in cognitive function when accompanied by diabetic complications, such as peripheral neuropathy [28,35]. One study has reported that diabetic retinopathy in men, but not in women, was associated with a decrease in cognitive performance [28]. The duration of type 2 DM and chronic hyperglycemia were associated with changes in cognitive function [8,36] (Fig. 2).

Some reports have shown that impaired glucose tolerance before DM was a risk factor of cognitive decline [37]. Numerous studies have shown that patients with impaired glucose tolerance had lower Mini-Mental State Examination and long-term memory scores [36], decreased verbal fluency [38], and worse Alzheimer’s dementia [20] and vascular dementia [19] than control subjects. However, not all studies obtained similar results.

**Pathophysiology of cognitive dysfunction in diabetes mellitus**

Thus far, the underlying pathophysiology of cognitive dysfunctions in DM is not well understood. However, several hypotheses have been proposed, and research results that validate such hypotheses have been published.

First, there is a hypothesis that cognitive dysfunction is correlated to hyperglycemia. Although hyperglycemia may be associated with decreased cognitive function in type 1 and 2 DM, the mechanism by which hyperglycemia mediates is still unclear. In other organs, hyperglycemia affects function by the following mechanism: polyol pathway activation, increased formation of advanced glycation end products, diacylglycerol activation of protein kinase C, and increased glucose shunting in the hexosamine pathway [39-42]. Several studies have indicated that the same mechanisms may work in the brain.

Second, there is a hypothesis that vascular disease plays an important role. Patients with DM are 2–6 times more likely at risk of thrombosis, which contributes to cognitive dysfunction [43-45]. Thickening of capillary basement membranes (the hallmark of diabetic microangiopathy) is also found in the brain of patients with DM [46]. The duration of illness was associated with the decreased global rates of cerebral blood flow in patients with DM. Interestingly, the cerebral blood flow rate of patients with DM is similar to that observed in patients with AD [47]. The coexistence of ischemia and hyperglycemia was considered detrimental to the brain. One potential mechanism by which hyperglycemia may enhance ischemic damage is lactate accumulation [48]. Hyperglycemia produces more substrate for the formation of lactic acid, causing cellular acidosis and exacerbated damage. Another mechanism is glutamate accumulation in the context of hyperglycemia and ischemia [49,50].

Third, whether hypoglycemic episodes contribute to cognitive impairment is controversial, and it may depend on the patient’s

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**Fig. 2. Factors affecting cognitive dysfunction in type 2 DM.** Chronic hyperglycemia, long duration of diabetes, presence of vascular risk factors (e.g., hypertension and obesity), and microvascular and macrovascular complications are associated with an increased risk of developing cognitive dysfunction in type 2 DM. Some authors have claimed that AD is type 3 DM with a combination of insulin deficiency and insulin resistance, particularly in patients with sporadic AD without the APOE e4 allele. DM, diabetes mellitus; AD, Alzheimer’s disease; APOE, apolipoprotein E.
age. However, extremely long-term severe hypoglycemia causes brain damage and even death \[45\]. In animal models, blood glucose levels of 0.12–1.36 mmol/L for 30–60 min lead to increased extracellular aspartate levels, alkalemia, and nerve necrosis with nerve energy damage, thereby resulting in a flat electroencephalograph result \[51\]. The cortex, basal ganglia, and hippocampus may be most vulnerable to hypoglycemia, and autopsies performed in human patients who died from hypoglycemia showed lamellar necrosis and gliosis in these areas \[52\]. Other human autopsy studies conducted after death secondary to hypoglycemia have shown multifocal or diffuse necrosis of the cerebral cortex and chromatolysis of ganglion cells \[53\]. Some researchers have hypothesized that hypoglycemia-induced neuronal damage occurs due to the overactivation of the excitatory neurotransmitter subtypes of the N-methyl-D-aspartate receptor (NMDA) receptor \[54\]. Interestingly, NMDA receptor antagonists prevent neuronal necrosis, indicating a potential treatment for hypoglycemia-induced brain injury \[55\].

Fourth, in recent studies, insulin resistance has been considered a mechanism of cognitive decline in patients with DM. In fact, historically, the brain was believed to be an insulin-independent organ. However, recent studies have questioned such a concept. There is a growing body of evidence showing that insulin resistance can play an important role in the pathogenesis of AD. Since glucose is the main fuel of the brain, the brain is starved due to the lack of glucose uptake and utilization. Insulin stimulates brain glucose uptake and utilization, metabolism, memory, and cognition. Insulin resistance/deficiency induces impairments in glucose metabolism and disrupts brain energy balance, thereby increasing oxidative stress, production of reactive oxygen species, deoxyribonucleic acid damage, and mitochondrial dysfunction, all of which drive pro-apoptosis, pro-inflammatory, and pro-amyloid-beta (Aβ) cascades \[56\]. Therefore, insulin and insulin-like growth factor (IGF) signaling pathways play critical roles in brain functions, such as cognitive functions in the central nervous system (CNS). Insulin, IGF-1 and IGF-2 polypeptides, and receptor genes are expressed in neuronal and glial cells throughout the brain. Their highest levels are in structures that are strongly targeted by neurodegeneration, particularly in AD \[56-58\]. Correspondingly, experimental depletion or suppression of brain insulin receptor expression and function causes cognitive dysfunction and the molecular and biochemical abnormalities observed in AD \[59\]. In this context, it is argued that AD is considered a brain disease with complex features of type 1 (insulin deficiency) and type 2 (insulin resistance) DM. To consolidate this concept, numerous investigators have proposed that AD should be referred to as type 3 DM \[60,61\].

**Evidence of type 3 diabetes mellitus in Alzheimer’s disease**

Sporadic AD as the cause of Aβ accumulation, which accounts for more than 90% of AD cases, is not yet well understood. Recent evidence has indicated that insulin/IGF resistance in the brain as both a cause and outcome. Insulin stimulation promotes the transport of Aβ from the trans-Golgi network from which it is derived to the plasma membrane for extracellular secretion \[62\]. Furthermore, insulin inhibits intracellular accumulation of Aβ and degradation by insulin-degrading enzymes \[63,64\]. Impaired insulin signaling disrupts amyloid-beta precursor protein peptides (AβPP) processing and AβPP-Aβ clearance in the brain \[65\].

The tau pathology is a representative neuropathological finding of AD along with Aβ. Moreover, studies have shown that insulin resistance affects tau expression and phosphorylation. Tau expression and phosphorylation are regulated by insulin and IGF \[66,67\]. In AD, brain insulin and IGF resistance impair signaling through phosphoinositol-3-kinase (PI3K), Akt, and Wnt/β-catenin and promote glycogen synthase kinase-3 beta (GSK-3β) activation. Overactivation of GSK-3β is responsible for tau hyperphosphorylation, which promotes tau misfolding and fibril aggregation.

The strongest evidence supporting the notion of type 3 DM in AD was from an experimental study of rats that received streptozotocin, a pro-diabetic drug, via intracerebroventricular injection. Streptozotocin-treated rats develop cognitive dysfunctions as characterized by lack of spatial learning and memory, brain insulin resistance and deficiency, and AD-like neurodegeneration \[68,69\]. Targeted exposure to pro-diabetic agents can cause neurodegeneration with structural, molecular, biochemical, and functional abnormalities that closely mimic the pathology of AD in humans. In particular, streptozotocin is a nitrosamine-related compound that can be found in processed and preserved foods, and it causes cognitive impairment, AD-type neurodegeneration, and brain insulin resistance with experimental exposures to low, sub-mutagenic doses. Some authors have shown that over the last few decades, western populations have been constantly presenting with increasing levels of exposure to nitrosamines due to constant and gradual contact with nitrates and nitrites in the environment, agriculture, and food resources, and this has recently been linked to the increased incidence of dementia \[68,69\].

Some studies have indicated that insulin resistance affects neurotransmission and memory formation. Streptozotocin-induced diabetic rats have reduced acetylcholine production and release as compared to control rats \[70\]. A mouse model in which cholinergic activity is blocked by scopolamine experienced memory loss and hyperactivity, a deficit that may be reversed by glucose
administration [71]. Moreover, glucose administration with elevated endogenous insulin levels or insulin administration to patients with AD has also been shown to cause changes in behavior, possibly by enhancing cholinergic activity [72]. DM and insulin may affect long-term potentiation in the opposite way. Long-term potentiation is important for memory formation and is induced by NMDA receptor activation, a process that is upregulated in the presence of insulin. However, rats presumed to have DM and relative insulin deficiency has reduced long-term potentiation in the hippocampus as measured via electrophysiology [73, 74]. Thus, brain insulin resistance in AD may require a higher level of insulin to stimulate memory [75]. However, it is unclear whether the direct effect of insulin is directly or indirectly influenced by other mediators [76].

Recently, a noteworthy report has indicated that the relationship between insulin resistance and cognitive impairment in AD is dependent on the presence or absence of the apolipoprotein E (APOE)-ε4 allele. The presence of the APOE-ε4 allele increases the risk of AD by a factor of 2–8, which plays a rather opposite role in the development of AD associated with insulin resistance. Insulin resistance is only an important risk factor of AD in patients without the APOE-ε4 allele [20]. Participants with AD without the APOE-ε4 allele also had improved memory scores in the hyperinsulinemic setting, which was not the case for APOE-ε4 allele-positive participants [77] (Fig. 2).

One of the important reasons for the active research in these fields may be the anticipation that antidiabetic drugs may play a preventive or therapeutic role in AD, which is known to have no cure. It has been hypothesized that neurodegeneration and cognitive dysfunctions in AD may be reduced or prevented with the early treatment of insulin-sensitizer antidiabetic agents, such as peroxisome proliferator-activated receptor (PPAR) agonists. Studies have reported that the PPAR agonist treatments prevent cerebral atrophy, preserve insulin and IGF-2 receptor-bearing CNS neurons, and specifically prevent it from ic-streptozotocin-induced deficits in learning and memory [78]. Some trials have shown that rosiglitazone, a PPAR-gamma, have a beneficial effect on memory in patients with AD. In a small randomized study published by Watson et al. [79] in 2005, patients with mild AD who were treated with rosiglitazone for 6 months had better memory and selective attention than the controls. A larger study published in 2006 has shown improvement in cognitive function after the administration of rosiglitazone for 6 months in patients with AD without the APOE-ε4 allele. However, no improvements were observed in patients with AD with the APOE-ε4 allele [80]. Similar studies have been conducted. However, the results remained inconsistent reports. The results of the systematic review and network meta-analysis [81] in 2018 have shown the significant effects of antidiabetic agents on AD and mild cognitive impairment, and pioglitazone 15–30 mg was more effective than placebo in a network meta-analysis.

**Conclusion**

Several studies about cognitive dysfunctions in patients with type 1 and type 2 DM have been conducted, and the results were inconsistent. Although some studies obtained conclusions, limitations were still observed. Type 1 DM has been associated with a decrease in the speed of information processing, psychomotor efficiency, attention, mental flexibility, and visual perception, and type 2 DM has been associated with memory deficits, a decrease in psychomotor speed, and reduced frontal lobe/executive function. Improved glycemic control and decreased diabetic complications may be associated with the prevention of cognitive dysfunction. However, the benefits of intensive glucose control in type 2 DM remain unclear. Severe hypoglycemic episodes may not have a long-term cognitive impact. However, it may cause cognitive impairment in high-risk patients diagnosed with DM (<4 years). The underlying pathophysiology is not well understood. Some authors have claimed that AD is type 3 DM with a combination of insulin deficiency and resistance particularly in patients with sporadic AD without the APOEε4 allele. However, results of previous studies remained inconsistent, and more consistent results must be obtained. If a patient reports that their performance is worsening or if they ask about the effects of DM on functioning, screening and assessment are recommended.

**Conflicts of interest**

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

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Cognitive dysfunctions in diabetes


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Current status of stereotactic body radiotherapy for the treatment of hepatocellular carcinoma

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Stereotactic body radiotherapy (SBRT) is an advanced form of radiotherapy (RT) with a growing interest in its application in the treatment of hepatocellular carcinoma (HCC). It can deliver ablative radiation doses to tumors in a few fractions without excessive doses to normal tissues, with the help of advanced modern RT and imaging technologies. Currently, SBRT is recommended as an alternative to curative treatments, such as surgery and radiofrequency ablation. This review discusses the current status of SBRT to aid in the decision making on how it is incorporated into the HCC management.

Keywords: Hepatocellular carcinoma; Image-guided radiotherapy; Radiotherapy; Stereotactic body radiotherapy

Introduction

Liver cancer is the sixth most common cancer and the second leading cause of cancer-related mortality in Korea [1]. Hepatocellular carcinoma (HCC) is the major histologic type of primary liver cancers, accounting for 70–85% [2], and has the highest mortality rate among major cancers in Korea [3]. Current treatment guidelines for HCC recommend surgical resection, liver transplantation, and radiofrequency ablation (RFA) as standard treatment options for small HCCs [4,5]. However, hepatic resection is possible in only < 30% of patients due to multifocal disease, unfavorable location, or inadequate functional hepatic reserve, and liver transplantation is associated with many hurdles such as donor availability [6]. RFA is not always safe or effective depending on the tumor size or locations [7].

Stereotactic body radiotherapy (SBRT), or stereotactic ablative radiotherapy, is an advanced form of radiotherapy (RT) that can deliver ablative radiation doses to tumors in a few fractions without excessive doses to normal tissues with the help of advanced modern RT and imaging technologies [8]. Several case series on SBRT have reported high local control rates of over 80% [9]. Current treatment guidelines for HCC recommend SBRT when other liver-directed therapies have failed or are contraindicated [4,5,10]. In addition, it is tried to be combined with other locoregional or systemic therapies.

However, radiation-induced complications in the liver and gastrointestinal (GI) tract prevent the use of SBRT. Patients with HCC often have cirrhotic liver with poor baseline liver function or less recovery ability, which could be related to a higher incidence of radiation-induced liver disease (RILD). The GI tract near the tumors often prevents high-dose irradiation from being delivered to the tumors. Respiratory movement of the liver containing tumors prevents the safe use of SBRT. For these reasons, various efforts have been implemented to understand the risk of toxicities and determine solutions.

This review discusses the current status of SBRT for HCCs in...
terms of technical and clinical aspects to help in the decision making of using SBRT while treating patients with HCC.

**Radiotherapeutic considerations**

1. **Process of stereotactic body radiotherapy**

The first step of treatment planning is acquisition of planning computed tomography (CT) images in the treatment position. Immobilization devices, such as stereotactic body frame and vacuum cushions, are usually used to improve the positional reproducibility and reduce the possible movement during the long treatment time of SBRT. Four-dimensional CT (4D-CT) scan with intravenous contrast media is usually used to identify tumor and normal organ movements during respiration. Depending on methods used for tumor localization and respiratory control during treatment, planning CT scans can be performed in various settings: free breathing or breath-hold with or without abdominal compression.

After transferring CT images to the RT treatment planning system, target volumes and normal organs are delineated. Gross tumor volume (GTV) is defined as the tumor(s) seen on imaging studies. In cases of invisible tumor(s) or unclear tumor margin on planning CT images, rigid or deformable registration with diagnostic CT or magnetic resonance imaging (MRI) can be used. The clinical target volume for SBRT is usually the same as for GTV, even though microscopic tumor extension might exist up to several millimeters. The internal target volume (ITV) is the sum of GTVs in all respiratory phases (or some predefined phases for respiratory gating). Planning target volume (PTV) is generated by adding a margin of about 5 mm (up to 10 mm) to ITV [11]. Thereafter, treatment plans are generated while considering tolerance doses of normal organs, especially for the normal liver and GI tract. Typically, 40–50 Gy in 3–5 fractions is prescribed to encompass the edge of PTV [11-14].

Immediately before treatment, the patient and tumor position are verified with orthogonal radiographs or cone-beam CT scans using various surrogate markers, such as the diaphragm, surgical clips, residual lipiodol after transarterial chemoembolization (TACE) or fiducial markers inserted a few days before planning CT. Recently, the MRI device integrated into the RT machine can be used for real-time tumor tracking during treatment. Finally, treatment starts with respiratory motion management such as active breathing control [15], abdominal compression [16], respiratory gating, and real-time tumor tracking. Respiratory gating is a technique that can treat tumors only at predefined respiratory phases. Tumor-tracking technique is thought to be an ideal method to treat moving targets, which can treat the tumors with the smallest PTV compared to other methods. With the proper use of these techniques, SBRT-related toxicities in the liver and GI tract can be minimized while ensuring enough doses to tumors.

Various imaging tools described above are used to maximize the accuracy and precision throughout the whole process, which is called image-guided radiotherapy (IGRT). The technical aspects of RT for HCC are discussed in detail elsewhere [17,18]. Fig. 1 shows an example of SBRT using tracking intensity-modulated beams.

2. **Tumor dose**

Radiation oncologists have used various dose fractionation schedules and investigated the impact of total dose and tumor size. For small tumors of < 3 cm (or < 5 cm), a high local control of > 90% has been achieved with a biologically effective dose (BED) of ≥ 100 Gy$_{10}$ (e.g., 50 Gy in 5 fractions or 45 Gy in 3 fractions), which is considered as an ablative dose [12,19,20]. BED, using a conventional linear-quadratic model assuming α/β of 10 Gy, was calculated as follows: BED = nd (1+d/[α/β]), where n is the number of fractions and d is the fraction size. In a retrospective study that escalated the radiation dose from 45 Gy in 3 fractions to 60 Gy in 3 fractions for HCCs of < 3 cm, no difference in local control was found between the 2 dose groups [20]. In contrast, several studies have reported lower local control rates in larger tumors [12,19,21]. Although Jang et al. [21] revealed that large tumors needed a higher radiation dose for the same tumor control probability of 90% as small tumors (51.1 Gy in 3 fractions for tumors of ≤ 5 cm vs. 62.1 Gy in 3 fractions for tumors of > 5–7 cm), higher radiation doses would inevitably increase the liver dose related to liver toxicity. Sanuki et al. [13] achieved a high 3-year local control rate of 91% with relatively low doses (40 Gy in 5 fractions in Child–Pugh [CP] A and 35 Gy in 5 fractions in CP B). A pooled analysis of 25 studies on SBRT revealed that overall survival was not different according to radiation doses (equivalent dose in 2 Gy per fractions [EQD2] using the α/β ratio of 10 Gy: < 80 Gy vs. > 80 Gy), where all available median EQD2 estimates ranged from 47.9 Gy to 100 Gy with a median of 83.3 Gy (equal to 100 Gy$_{10}$ in BED) [9]. Therefore, considering that higher radiation dose and/or larger tumor volume could increase hepatic and/or GI toxicities, the risk adaptive dose–fractionation regimens would be useful to balance both tumor control and toxicities, especially in patients with poor liver function.

3. **Charged particle therapy**

Charged particles such as proton or carbon ions have a unique beam profile known as Bragg peak, which can prevent irradiation of normal tissues beyond the tumor. Treatment outcomes in patients with HCC treated with proton or carbon ions are promis...
Fig. 1. An example of stereotactic body radiotherapy using tracking intensity-modulated beams for a 20-mm-sized lesion in segment 1 that occurred after right hepatectomy and 5 times of radiofrequency ablation. (A) Gold fiducial markers are inserted before the simulation for patient/tumor position verification and real-time tumor tracking. (B, C) Target volumes and normal tissues are delineated in breath-hold images, and then treatment plan using 9 intensity-modulated beams is generated (gross tumor volume in red, planning target volume in cyan, and the intestine in green). (D) In the treatment room, locations of fiducial markers are verified using cone-beam computed tomography. (E) The treatment beams are delivered while monitoring the movement of the fiducial markers in real time. Electronic portal imaging device shows the movement of each beamlet during tracking treatment. Images in B, C, and E are from this patient, and images in A and D are from other patients for demonstration.
Clinical considerations

1. Clinical outcomes of stereotactic body radiotherapy

Many institutions have reported their clinical outcomes after SBRT for HCC after the first report by Blomgren et al. [26]. Even though dose schedules and patient/tumor characteristics were heterogeneous, clinical outcomes were promising in terms of tumor control and toxicities. Recently, Rim et al. [9] conducted a meta-analysis on the results of 32 studies, including 1,950 patients, published in between 2010 and 2018. The median proportion of CP A was 82.3% (range, 47.9–100%). The median of the median tumor sizes was 3.3 cm (range, 1.6–8.6 cm). The median of the median EQD2 estimates was 83.3 Gy (range, 48.0–114.8 Gy). Pooled 1-, 2-, and 3-year overall survival rates were 72.6% (95% confidence interval [CI], 65.7–78.6), 57.8% (95% CI, 50.9–64.4), and 48.3% (95% CI, 40.3–56.5), respectively. Pooled 1-, 2-, and 3-year local control rates were 85.7% (95% CI, 80.1–90.0), 83.6% (95% CI, 77.4–88.3), and 83.9% (95% CI, 77.6–88.6), respectively. Larger tumor size of ≥ 5 cm was a significant factor for worse local control and overall survival rates. Hepatic and GI complication rates of grade ≥ 3 were 4.7% (95% CI, 3.4–6.5) in a pooled analysis of 23 studies, which was comparable high [27,28]. SBRT was notably achieved a lower local control rate than RFA for tumors of ≥ 2 cm in Wahl et al.’s study [28], which may be related to the better radiation dose coverage of SBRT and limited heat transfer to long distances from the heat source of RFA. In addition, tumor control was not influenced by the tumor size after SBRT in two studies with a median tumor size of 2.2 cm (range, 0–10.0 cm) and 7.2 cm (range, 1.4–23.1 cm) [28,29], which implies that SBRT could be a preferred treatment option for large tumors.

RFA is less effective or contraindicated in the following situations: tumors close to the major vessels (due to the heat sink effect); tumors abutting the diaphragm (due to the risk of diaphragmatic injury); tumors on the liver capsule (due to the risk of rupture or track seeding); centrally located tumors (due to the risk of bile duct injury); and invisible tumors on ultrasonography [30]. Instead, SBRT is less influenced by tumor location, except its distance from the GI tract.

An important difference between RFA and SBRT is repeatability. In contrast to RFA, repeated use of SBRT is limited for new HCC lesions due to the decreased liver function after SBRT [31]. Considering that frequent intrahepatic recurrences of HCC require repeated treatments, SBRT might be spared for lesions unsuitable for other liver-directed treatments. In contrast, Lee et al. [32] reported the treatment outcomes after a repeated SBRT for recurrent HCCs with a median tumor size of 1.7 cm (interquartile range, 1.4–2.2 cm) in 85 patients. The 3-year local control rates were not different between the first and second SBRT (94.9% vs. 90.4%, p = 0.667). None of the 73 patients with CP A experienced RILD after the second SBRT, whereas 2 of the 12 patients with CP B experienced irreversible liver function deterioration. Although the use of repeated SBRT has been limited so far, SBRT can be reapplied to highly selected patients with good liver function.

The superiority in the survival aspect between SBRT and other treatments has been controversial. RFA showed superior survival compared to SBRT in a study based on a large number of patients from the National Cancer Database [33]. When comparing SBRT with surgical resection, survival was comparable or superior in the surgery group, depending on the studies [34,35]. However, a firm conclusion cannot be made because of both the retrospective design and potential selection bias in these studies.

2. Selection of local modalities

Tumors unsuitable for ablation or surgical resection or with failed treatments have usually been treated with SBRT; however, deciding whether a patient is a proper candidate for SBRT or which is the best modality is difficult. Data below would help the multidisciplinary team to recommend SBRT for a given patient, even though the evidence level is low.

Overall local control rates of SBRT and RFA have been reported to be comparably high [27,28]. SBRT was notably achieved a higher local control rate than RFA for tumors of ≥ 2 cm in Wahl et al.’s study [28], which may be related to the better radiation dose coverage of SBRT and limited heat transfer to long distances from the heat source of RFA. In addition, tumor control was not influenced by the tumor size after SBRT in two studies with a median tumor size of 2.2 cm (range, 0–10.0 cm) and 7.2 cm (range, 1.4–23.1 cm) [28,29], which implies that SBRT could be a preferred treatment option for large tumors.

Liver toxicities, or RILD, is the most important dose-limiting factor for the treatment of liver tumors [36]. Patients with HCC are more vulnerable to the development of RILD because HCC frequently occurs in a cirrhotic liver susceptible to radiation injury. Non-classic RILD (elevation of liver transaminases or decline of CP score) is usually reported after SBRT, rather than classic RILD (anicteric hepatomegaly and ascites or elevation of alkaline phosphatase). The RILD rate of grade ≥ 3 was as low as 4.7% (95% CI, 3.4–6.5) in a pooled analysis of 23 studies, which was
generally transient [9]. Since worse baseline liver function is correlated with higher risk of severe RILD [13,37-40], caution is warranted in deciding the treatment and SBRT planning in patients with poor liver function. Although no definite guidelines were available for liver constraints, the following guidelines have been used: limiting SBRT to CP A or B7 patients [5]; adjusting prescription dose using the normal tissue complication probability of the liver [39]; limiting the normal liver dose (e.g., mean normal liver dose: < 13–18 Gy in 3–6 fractions for CP A vs. < 6 Gy in 4–6 fractions for CP B) [36]; or sparing the critical residual liver volume (e.g., ≥ 700 mL of normal liver receives ≤ 15 Gy in 3–5 fractions) [36].

2. Gastrointestinal tract
Because tolerance doses of luminal structures such as the esophagus, stomach, or intestine are much lower than ablative doses used for SBRT, special concerns are required for lesions close to luminal structures. In one case series, all 5 patients who experienced grade 3 or 4 GI toxicities had lesions within 0–0.4 cm from the GI tract [21]. Radiation oncologists generally recommend SBRT for lesions with enough distance from GI tract (e.g., > 1–2 cm) [14,41]. To overcome this limitation, various techniques are attempted, including 4D-CT, abdominal compression, gated RT, tracking RT, or intensity-modulated beam. Real-time tumor tracking, using fiducial markers (Fig. 1A) or MRI images, is the current most advanced method used to avoid the GI tract close to tumors. Fig. 1 shows an example of a patient undergoing follow-up without GI complication at 33 months after receiving tracking SBRT for a tumor at 5 mm from the bowel. Tolerance doses of luminal structures are discussed in detail elsewhere [42-45].

3. Bile duct
Biliary stricture has been occasionally reported at the rate of 0–3% [12,28,32,46-48]. Eriguchi et al. [49] found biliary stenosis in 2 out of 50 patients irradiated with over 20 Gy to the central biliary system; 1 patient experienced biliary stricture at the area irradiated with > 80 Gy after the second SBRT and the stenotic site of the other patient was outside the area irradiated with > 20 Gy. In addition, even in a study that investigated the relationship between the central hepatobiliary tract dose and hepatobiliary toxicity rate (not only for biliary tract complications), no biliary stricture was observed in 20 patients with HCC unlike the intrahepatic cholangiocarcinoma with high rate of biliary stricture (38.8% of 26 patients) [50]. Therefore, SBRT seems to be a feasible modality for centrally located tumors unsuitable for other treatments.

Additional indications of stereotactic body radiotherapy

1. As a bridge therapy
Bridge therapies can be used to prevent tumor progression while waiting for transplantation or to downstage tumors into the Milan criteria. SBRT as a bridge therapy has also been reported as safe and effective. O’Connor et al. [51] and Andolino et al. [52] reported that SBRT did not increase surgical complications. Saprischin et al. [53] revealed that drop-out, post-transplant survival, and HCC recurrence rates after liver transplantation were similar among SBRT, TACE, and RFA. Mohamed et al. [54] showed that acute toxicities of SBRT and yttrium-90 radioembolization were lower than those of TACE or RFA. These results suggest that SBRT is a viable option as bridge to transplantation.

2. In advanced hepatocellular carcinoma
HCC with portal vein tumor thrombosis (PVTT) has poor prognosis; however, the standard treatment strategy remains to be established. RT has been used to restore the portal flow and facilitate subsequent treatments such as surgery or TACE. The response rate was 39–57% with conventional RT using a small fraction size of 1.8–3 Gy, which requires a long treatment period (e.g., 45–50 Gy in 25 fractions over 5 weeks) [55]. Advanced RT techniques such as intensity-modulated RT or IGRT facilitate giving higher radiation doses without increasing GI toxicities, with which higher tumor response and better survival would be expected [56]. Although advanced tumor characteristics related to PVTT, poor liver function, or close distance to GI tract often limit the use of SBRT for PVTT [57], recent studies have reported high PVTT response rates (70–76%) after SBRT using relatively low dose regimens (e.g., 40 Gy in 5–6 fractions over 1–2 weeks) [58-60]. Therefore, SBRT, which ends in a short treatment period, is worth of future investigation for the treatment of PVTT, especially in combination with recently developed systemic agents.

Large or multiple HCCs not suitable for curative treatments are often treated with TACE with or without RT [4,5]. A meta-analysis by Meng et al. [61], comparing TACE plus RT to TACE alone, revealed that the adding RT to TACE improved the tumor response and survival, where small doses per fraction and lower total doses were usually used for fear of toxicities in the liver and GI tract. As SBRT has a higher capability of sparing normal tissues as compared to RT techniques used before, SBRT could be assumed to increase the clinical outcomes when combined with TACE for large HCCs. Jacob et al. [62] reported that TACE plus SBRT (45 Gy in 3 fractions) achieved better local
control and survival rates than TACE alone in HCCs of ≥ 3 cm. Paik et al. [63] confirmed the comparable survival outcomes among the three treatment groups (complete TACE alone, incomplete TACE followed by curative treatments, and incomplete TACE followed by SBRT [46–60 Gy in 3–5 fractions]). These results imply that SBRT is an effective adjuvant treatment for HCCs showing an incomplete response to TACE.

3. In combination with systemic therapies

Despite the high local control rates of SBRT, there is a demand to combine SBRT with systemic agents due to frequent intrahepatic or extrahepatic recurrences after SBRT. Sorafenib, a multikinase inhibitor, was attempted to be combined with SBRT based on improved overall survival in patients with advanced HCC treated with sorafenib (vs. best supportive care group) in SHARP phase III trial [64] and in vitro and in vivo radiosensitising effect of sorafenib in HCC cell lines [65]. However, the addition of sorafenib to SBRT is not currently recommended due to increased risk of GI toxicities [66,67].

Recently, immunotherapy has been successfully employed for the treatment of solid tumors such as melanoma and non-small cell lung cancer, and the combination of immunotherapy with RT is an active field of clinical investigation [68]. SBRT using a high radiation dose per fraction is known to have an immunomodulatory effect, which can potentially improve tumor response and survival outcomes of immunotherapy [69]. Notably, abscopal effect, or tumor regression outside the RT field, has been increasingly reported when RT was combined with immunotherapy, even though it was a rare phenomenon before the era of cancer immunotherapy. Mechanisms of abscopal effect, related to systemic effect of radiation, are also being revealed [70,71]. In 2017 and 2018, 2 immune checkpoint antibodies, nivolumab and pembrolizumab, have been approved to be used as a second-line therapy for HCC by the Food and Drug Administration. Preclinical data showed that the combination of programmed death ligand 1 blockade and RT significantly suppressed the tumor growth in a murine HCC model compared with single treatments [72]. And, there are several ongoing phase I or II trials combining immunotherapy and SBRT for patients with HCC (NCT03203304, NCT0316872, NCT03482102, and NCT03817736). With this new strategy, the prognosis of both early and advanced HCCs is anticipated to improve via enhanced local and systemic effects.

Conclusion

Current evidences support the use of SBRT as an alternative or complement to curative treatments based on its high local control rates and low toxicity profiles. There is also an emerging interest in combining SBRT with other locoregional or systemic therapies to potentially maximize treatment outcomes. Clinical uses of SBRT are summarized in Table 1. However, optimal dose–fractionation regimens balancing tumor control and toxicities and methods to overcome the current limitations of SBRT should be determined. Given that clinical presentations of patients with HCC are significantly heterogeneous, a multidisciplinary team approach could determine the best candidates who would benefit from SBRT with or without combined treatments.

Conflicts of interest

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

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Table 1. Clinical uses of stereotactic body radiotherapy for hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Use of SBRT</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>1. Recommended by major guidelines for HCC management</td>
<td>- As an alternative to curative treatment options for single tumors or multiple small lesions with a limited number (BCLC stage 0–A)</td>
</tr>
<tr>
<td>2. Based on small case series</td>
<td>- As a bridge therapy to prevent tumor progression or to downstage tumors into the Milan criteria</td>
</tr>
<tr>
<td>3. Promising</td>
<td>- As adjuvant therapy after incomplete transarterial chemoembolization for large tumors (BCLC stage A) or multiple lesions (BCLC stage B)</td>
</tr>
<tr>
<td>4. - As palliative therapy to restore the portal flow and facilitate subsequent treatments in HCC with portal vein thrombosis (BCLC stage C)</td>
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HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer.
tics according to sex and severity levels in Korea. PLoS One 2018;13:e0203110


Implant-based breast reconstruction is the most commonly used reconstruction technique after mastectomy. This is because skin-sparing mastectomy has become possible with advancements in oncology. In addition, the development of breast implants and the advent of acellular dermal matrices have reduced postoperative complications and resulted in superior cosmetic results. The most frequently performed surgical breast reconstruction procedure for the past 20 years was the insertion of an implant under the pectoralis major muscle by means of the dual plane approach. However, some patients suffered from pain and animation deformity caused by muscle manipulation. Recently, a prepectoral approach has been used to solve the above problems in select patients, and the results are similar to subpectoral results. However, this technique is not always chosen due to the number of considerations for successful surgery. In this article, we will discuss the emergence of prepectoral breast reconstruction, indications and contraindications, surgical procedures, and outcomes.

**Keywords:** Acellular dermal matrix; Breast implants; Mastectomy; Prepectoral breast reconstruction

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**Introduction**

Breast reconstruction is increasing every year alongside increases in breast cancer. According to American Society of Plastic Surgeons statistical report, the numbers of breast reconstructions in the United States in 2000 and 2018 were 78,832 and 101,657, respectively [1]. The most frequently used reconstructive method is an implant-based reconstruction. In 2018 in the United States, 83,216 implant-based reconstructions were performed, while 18,441 autologous tissue reconstructions were done [1]. Prosthetic breast reconstruction is the number one procedure because advancements in implants and improvements in mastectomy techniques have resulted in better aesthetic outcomes. Recently, an issue has arisen regarding which plane implants should be placed in. In other words, a reverse shift from submuscular to prepectoral placement has occurred.

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**History**

The ideal location for implants was once thought to be under the skin where the original breast tissue was, above the pectoralis major muscle. Silicone or saline implants were inserted subcutaneously until the introduction of the tissue expander. This approach was simple and able to preserve muscles, but typically, the mastectomy flap was too thin, and the subcutaneous tissue was deficient, resulting in many complications associated with this method. Implants that became exposed through the skin increased the risk of infection of the implants. Ultimately, removal of the implants occurred frequently, and capsular contracture, in particular, was a common complication [2]. These led to a submuscular approach where the implants were completely covered by the pectoralis major and serratus anterior muscles using a prepectoral approach. Gruber et al. reported a comparison of submuscular and subcutaneous techniques for breast reconstruc-
tion following mastectomy [3] and concluded that submuscular implants are clearly superior to subcutaneous ones and that the subseratus techniques provided the lowest incidence of capsular contracture. Augmentation case studies have also concluded that the subpectoral approach is superior, especially in regard to capsular contracture [4,5].

However, the full muscle coverage technique has some problems. It could not expand the lower pole and natural ptotic breasts. In addition, implants were not covered by only the pectoralis major muscle, and the recruitment of other muscle flaps, such as the serratus muscle or the rectus abdominis sheath, was needed. To solve these problems, the partial muscle coverage, or dual plane, technique was introduced. This technique enabled expansion of the lower pole, but the pectoralis major muscle was not fixed to the chest wall, so it often migrated superiorly, resulting in so-called window shading [6-8].

These problems were addressed by the advent of acellular dermal matrices (ADMs). An ADM is a biotechnologically designed human tissue of bovine or porcine origin that has served numerous purposes across surgical subsectors. Tissue processing removes cellular antigens that can generate an immunological response while maintaining a structural matrix that promotes angiogenesis and tissue regeneration. In 1995, for the first time, ADM was used to treat full-thickness burns [9]. Then, in 2006, Salzberg published his experience using ADM in immediate breast reconstruction, and ADM became an important ingredient in breast reconstruction [10].

Afterward, the dual plane approach of ADM and covering the implant with the pectoralis major muscle was commonly performed. In this procedure, the ADM was sutured to the inferior margin of the pectoralis major muscle, which enabled not only expansion of the lower pole but also a decreased incidence of window shading. In addition, the ADM defines the lateral inframammary fold and supports the inferolateral portion, resulting to minimize migration of the implant caused by muscle contraction.

However, there still remain problems of animation deformity due to muscle contraction, as well as pain caused by the dissection of the muscle. Ultimately, plastic surgeons were reminded of the idea of inserting an implant in the site of the original breast tissue without operating again on the muscle. Notably, capsular contracture, which was the main complication of previous subcutaneous breast reconstruction procedures, has been reduced with the use of ADMs. Kim et al. reported that the levels of myofibroblasts were significantly lower in ADM capsules than in submuscular capsules [11]. Now, with advances in oncology such as the skin-sparing mastectomy with optimal skin flap, improved implants, and ADMs, prepectoral breast reconstruction has become feasible.

**Patient selection**

Prepectoral breast reconstruction has obvious advantages. In addition to the surgical technique being simple and less invasive, the operation time is short, and the muscle is left intact, reducing bleeding, pain, and recovery time after surgery. The biggest advantage is that it significantly reduces the occurrence of animation deformities. Because the contraction of the muscle does not affect the implant, there is less implant migration. Despite these advantages, the use of this method is limited because the appropriateness of the mastectomy skin flap after oncologic resection determines the viability of the operation. In other words, good vascularity and sufficient subcutaneous fat tissue should remain (Table 1) [12]. If the skin flap is too thin, it can cause rippling and palpability problems. If the vascularity is poor, skin necrosis, infection, and other complications may occur. Therefore, for successful surgery, it is important to select appropriate patients through close cooperation between the breast surgeon and the plastic surgeon.

Prepectoral breast reconstruction is especially recommended for athletes, who require extensive use of the pectoralis major muscle, or for those whose shoulder function should be preserved. However, this lifestyle alone cannot determine the operation. There are two major factors in play, one of which is adequate vascularization of the mastectomy skin flap, which can be assessed before and during surgery, and the other is the oncologic consideration.

Patient factors that may affect the vascularity of the skin flap before surgery should be considered (Table 2) [13,14]. Poorly controlled blood glucose, obesity, and recent smokers are contraindicated.

**Table 1. Indications of prepectoral reconstruction**

| Good perfusion of the mastectomy skin flaps |
| Athletes who require extensive pectoralis major use |
| Grade 1 or 2 ptosis, or volume of mastectomy specimen < 500 g |
| Low BMI (< 35 kg/m²) |
| Non- or ex-smokers |

BMI, body mass index.

**Table 2. Contraindications of prepectoral reconstruction**

| Poorly vascularized mastectomy skin flap |
| Active smokers/recent smokers |
| BMI > 40 kg/m² |
| Immunocompromised patients |
| HbA1c > 7.5% |
| Large tumors (> 5 cm) |
| Tumors within 0.5 cm of the pectoralis major muscle |
| Chest wall involvement |
| Grossly positive axillary involvement |

BMI, body mass index; HbA1c, hemoglobin A1c.
cations. Large breasts require large implants, resulting in a decrease of the perfusion of skin, so they are a contraindication. In addition, immunocompromised patients are at increased risk in general and are not suitable for this procedure. Another important factor is the irradiated status of the breast. Preoperative radiation therapy affects wound healing and increases rates of infection, skin necrosis, capsular contracture, and more. Instead of prepectoral breast reconstruction, it is recommended that these patients undergo autologous tissue reconstruction [15]. Although there are few studies related to prepectoral reconstruction and postmastectomy radiation therapy (PMRT), there are arguments that the prepectoral approach may be a more appropriate choice for patients receiving adjuvant radiation therapy than the dual plane approach. Sigalove et al. studied 33 patients who underwent 52 breast reconstructions via the prepectoral approach and the short-term outcomes. They concluded that an immediate implant-based prepectoral breast reconstruction followed by PMRT appeared to be well tolerated, with no excess risk of adverse outcomes [16].

According to Sinnott et al., patients undergoing submuscular breast reconstruction who received PMRT had a capsular contracture rate three times greater, with more severe contractures (Baker grade III or IV) than did patients receiving PMRT who underwent prepectoral breast reconstruction [17]. Sbitany et al. studied 26 breasts that underwent immediate prepectoral reconstruction and 31 breasts that underwent immediate submuscular/dual plane reconstruction in the setting of PMRT and found no significant differences in complication rates between the two reconstructive groups [18].

It is important to evaluate the condition of the skin flap intraoperatively, and there is a method for clinically or objectively evaluating whether the perfusion of a mastectomy skin flap is good or bad, which will be discussed in detail in the surgical technique section.

Another concern with prepectoral breast reconstruction is the problem associated with the detection of cancer recurrence. If the tumor is located close to the pectoralis muscle, with a subpectoral implant placement, a recurring tumor can be detected by palpation. However, with a prepectoral implant placement, tumor recurrence may be detected later. Therefore, the location of the tumor should be taken into consideration during prepectoral reconstruction.

Surgical technique

1. Assessment of mastectomy skin flap

Clinical examination is important for evaluating the vascularity of skin flaps (Fig. 1), and bleeding on the incision edge should be seen. Any subcutaneous fat should also be preserved because if there is only dermis and no fat, blood flow will be inadequate. In those cases, it is necessary to consider a dual plane placement or staged reconstruction rather than an immediate prepectoral placement. However, skin thinning is not necessarily contraindicated. Even with thin skin, if the subdermal plexus is preserved, prepectoral breast reconstruction is possible.

Another method of assessing tissue perfusion is the use of indocyanine green angiography. This can evaluate the blood flow of arterial and venous vasculature in real time and helps to confirm
the clinical examination. It is helpful to predict the viability of the skin flap, especially if the skin is expanded when the implant is placed, and it allows the surgeon to ensure that any skin flap expected to become necrotizing is removed.

2. Choice of implant and acellular dermal matrix
The implant in a prepectoral reconstruction should be carefully selected to prevent rippling. To do so, the selected implant must have a base width dimension that is correct for the pocket of the ADM or skin flap. The cohesiveness of the implant is determined by the thickness of the skin [19]. The thinner the flap, the better it is to choose a highly cohesive gel implant. Less cohesive gel implants are more prone to wrinkling but could be selected for better projection because there is more collapse at the upper pole and descent to the lower pole. However, whether round or smooth can be selected dependent on the operator’s preference and the patient’s desire.

With two-stage surgery, it is important to underfill the tissue expander to make the tight pocket in the second stage. The height of the expander is chosen depending on whether the implant is anatomic or round. Typically, short to medium height expanders are used in the first stage for planned round implants, and full height expanders are used for planned anatomical implants.

The ADM is typically used in prepectoral breast reconstruction, but it is not necessarily used [20]. It has been reported that there was no difference in complication rates between groups where an ADM was used and groups where it was not, but it is clear that the incidence of capsular contracture is significantly lower in the ADM group [21–26]. The selected ADM is usually 2–3 mm thick. If a perforated ADM is used, fluid can flow in both directions, minimizing sticking between the ADM and the skin flap. In addition, the perforations create an adhesive area between the ADM and the skin flap, thereby promoting incorporation [27].

3. Acellular dermal matrix coverage
There are various methods for covering an implant with an ADM [28], and there is some controversy whether it is better to use 1 large ADM sheet or to sew 2 or more sheets together. There is also controversy as to whether it is better to cover the implant only anteriorly or both anteriorly and posteriorly. The latter idea of total ADM coverage of the device has been assessed to demonstrate the lower incidence of capsular contracture [22,29]. Because ADMs are shaped in flat sheets and there are various sizes, there are more ways to cover the three-dimensional shape of implants. For example, Braxon (DECO med s.r.l., Marcon, Venice, Italy) is a pre-shaped, porcine, non-cross-linked ADM that can be wrapped around an implant.

There are two main ways to place an ADM in the prepectoral space, according to US Food and Drug Administration (FDA) labeling. The FDA requires that an ADM for breast reconstruction is used for tissue support. Therefore, with the on-label method, a trimmed ADM is inserted into the prepectoral space, and after insertion of the implant, the edges of the ADM are sutured to the inframammary fold along the chest wall, leaving a 3–4 cm cuff along the pectoralis major muscle. With this method, an inferior “gutter” is created to support the lower pole. In contrast, with the off-label technique, the ADM supports the implant. The implant is wrapped with the ADM on the back table, making a peripheral “cuff,” and then the device with the ADM is inserted in the prepectoral space. In this method, the implant is either partially (Fig. 2) or completely (Fig. 3) wrapped with ADM. Whichever option the operator chooses, it is important for a permanent implant to align the ADM to the shape of the implant without laxity. For an expander, it is possible to make an ADM pocket with a little laxity. After insertion of the device into the mastectomy pocket, the ADM is fixated to the underlying pectoralis major muscle circumferentially using absorbable sutures. In cases where a tissue expander is used, it is fixed to the pectoralis to anchor the expander tabs.

Outcomes
There is a lack of long-term outcomes for prepectoral breast reconstruction. However, several authors have reported on the safety, functional and aesthetic outcomes, and complications. Sigalove et al. published preliminary results from over 350 prepectoral breast reconstructions using ADMs [30]. Complications such as infection, seroma, and flap necrosis occurred at rates of less than 5%, and there were no capsular contractures. Patients with prior radiation therapy had higher rates of complications (5 out of 10). In contrast, patients with PMRT had no complications. Zhu et al. reported on comparative studies of prepectoral and total muscle coverage breast reconstruction [31] where they demonstrated similar morbidity rates with regard to infection, superficial skin necrosis, and seroma in both groups but decreased rates of capsular contracture in the prepectoral group. Bernini et al. examined the surgical and aesthetic results of 34 subpectoral and 39 subcutaneous techniques using titanium-coated polypropylene mesh [32]. Although there were no significant differences between the groups, the subcutaneous group had an implant failure rate of 5.1%, while the subpectoral group had a 0% failure rate. The subcutaneous group also had significantly better aesthetic outcomes.

Schaeffer et al. reported early functional outcomes following prepectoral breast reconstruction in comparison with subpectoral

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Fig. 2. Two sheets of fenestrated acellular dermal matrices are sewn together and draped over the implant (A). On the back, the implant is partially covered (B).

Fig. 3. The device is fully covered by 2 sheets of acellular dermal matrices (A). On the back, the implant is fully covered (B).

breast reconstruction [33]. They showed that the prepectoral groups had significantly lower inpatient pain scores. In addition, the range of shoulder motion in the prepectoral group had fully returned in half the number days as in the subpectoral group.

Rippling and wrinkling are commonly seen in the setting of prepectoral reconstruction. There is also a clear step-off between the chest wall and the prepectoral implant. Although there are very few studies about the effect of autologous fat grafting on patient reported outcomes following prepectoral breast reconstruction, many authors have argued that the primary means for correcting

https://doi.org/10.12701/yujm.2019.00283
these deformities is autologous fat grafting [13,30,34,35]. Advances in fat grafting techniques have made fat grafting a routine procedure in breast surgery [30]. In fact, in 2018 in the United States, nearly 30% of all breast reconstruction cases utilized autologous fat grafts [1]. This allows the soft tissue volume between the implant and the mastectomy flap to be supported and augmented.

The cost of ADM is an issue in the setting of prepectoral reconstruction. Two or 4 times the size of ADM that is used for subpectoral breast reconstruction is needed for this procedure, which will certainly result in incurring additional costs in a range of $5,000 to $20,000 per breast. However, some authors have claimed that prepectoral breast reconstruction is economically advantageous, but more studies should be performed [25,36]. For cost-savings, other authors have noted the use of alternative materials such as Vicryl mesh [21], porcine mesh [22], or titanium-coated polypropylene mesh [32]. All have demonstrated success in the prepectoral setting and may have cost-saving benefits.

**Conclusion**

Prepectoral breast reconstruction is a simple muscle-sparing technique that reduces pain and recovery time after surgery. Above all, the occurrence rate of animation deformities can be reduced. In addition, aesthetically superior outcomes have been demonstrated. A successful prepectoral approach is possible with appropriate patient selection, availability of ADM, and improved fat grafting techniques. However, more long-term outcomes of prepectoral breast reconstructions, especially with PMRT, are required, along with studies of the mechanisms allowing for decreases in capsular contracture with ADMs.

**Conflicts of interest**

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

**Patient consent**

Patient provided written consent for the use of her images.

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**References**

Feasibility and efficacy of coil embolization for middle cerebral artery aneurysms

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Background: The anatomy of middle cerebral artery (MCA) aneurysms has been noted to be unfavorable for endovascular treatment. The purpose of this study was to assess the feasibility and efficacy of coiling for MCA aneurysms.

Methods: From January 2004 to December 2015, 72 MCA aneurysms (38 unruptured and 34 ruptured) in 67 patients were treated with coils. Treatment-related complications, clinical outcomes, and immediate and follow-up angiographic outcomes were retrospectively analyzed.

Results: Aneurysms were located at the MCA bifurcation (n=60), 1st segment (M1, n=8), and 2nd segment (M2, n=4). Sixty-nine aneurysms (95.8%) were treated by neck remodeling techniques using multi-catheter (n=44), balloon (n=14), stent (n=8), or combination of these (n=3). Only 3 aneurysms were treated by single-catheter technique. Angiographic results were 66 (91.7%) complete, 5 (6.9%) remnant neck, and 1 (1.4%) incomplete occlusion. Procedural complications included aneurysm rupture (n=1), asymptomatic coil migration to the distal vessel (n=1), and acute thromboembolism (n=10) consisting of 8 asymptomatic and 2 symptomatic events. Treatment-related permanent morbidity and mortality rates were 4.5% and 3.0%, respectively. There was no bleeding on clinical follow-up (mean, 29 months; range, 6-108 months). Follow-up angiographic results (mean, 26 months; range, 6-96 months) in patients included 1 major and 3 minor recanalizations.

Conclusion: Coiling of MCA aneurysms could be a technically feasible and clinically effective treatment strategy with acceptable angiographic and clinical outcomes. However, the safety and efficacy of this technique as compared to surgical clipping remains to be ascertained.

Keywords: Coil embolization; Intracranial aneurysm; Middle cerebral artery

Introduction

The International Subarachnoid Aneurysm Trial (ISAT) data in 2002 led to a significant change in the treatment of intracranial aneurysms. Although the ISAT study had exclusively addressed ruptured intracranial aneurysms, their results were rapidly assimilated into the treatment of unruptured intracranial aneurysms [1].

However, there is still controversy about the treatment strategy for middle cerebral artery (MCA) aneurysms and surgical clipping is the preferred strategy, because MCA aneurysms are proximal to the cerebral surface and require less brain retraction to access and expose [2-4]. Moreover, endovascular coil embolization was likely to be unfavorable because MCA aneurysms often have wide necks and incorporate branches. Although some recent
studies have demonstrated that endovascular embolization is equivalent to surgical clipping for the treatment of selected MCA aneurysms, coiling of wide-necked MCA aneurysm still remains technically challenging [5-9].

However, newly developed devices and advanced neck-remodeling techniques using multi-catheter, balloon, stent, or a combination of these permit endovascular treatment (EVT) of complex aneurysms [9-12].

The aim of this study was to retrospectively analyze the feasibility and efficacy of EVT for ruptured and unruptured MCA aneurysms at a center where coiling is the first option considered.

Materials and methods

From January 2004 to December 2015, EVT was performed on 72 MCA aneurysms in 67 patients. Informed written consent was obtained from all patients in this retrospective study and approved by the Institutional Review Board of Kosin University Gospel Hospital (KUGH 2019-03-009).

Patient and aneurysm characteristics, angiographic and clinical outcomes, and follow-up were evaluated by the referring neurosurgeons and an interventional neuroradiologist. Decision regarding treatment type (clipping versus coiling) was made by a neurovascular team involving neurosurgeons and an interventional neuroradiologist after completion of initial digital subtraction angiography (DSA). In agreement with our neurovascular team, coiling was the first-line treatment for MCA aneurysms, unless associated with compressive hematoma requiring immediate surgical evacuation. An experienced interventional neuroradiologist determined the possibility of coil embolization for MCA aneurysms, taking into consideration their shape, size, length of the neck, and complexity. Wide-neck aneurysms were defined as having a large neck (more than 4 mm) or a dome-to-neck ratio less than 1.5. Complex MCA aneurysms were defined by using particular anatomic features, including a branch vessel arising from the aneurysm sac and wide neck aneurysm with parent vessel incorporation.

Inclusion criteria for this study were (1) ruptured MCA aneurysm, (2) unruptured MCA aneurysm ≥ 7 mm in size, (3) unruptured MCA aneurysm < 7 mm in size with risk factors for aneurysm rupture such as previous or family history of subarachnoid hemorrhage (SAH), presence of lobulation or daughter sac, increased size on follow-up study, or multiple intracranial aneurysms, (4) patient criteria including young age, long life expectancy, and patients’ preferred treatment modality, or (5) recurred MCA aneurysm after coiling or clipping. The ruptured patients group was classified according to the Hunt and Hess grading scale (HHGS) to determine the clinical severity of the SAH. The modified Rankin scale (mRS) score was used to assess the clinical results recorded at each patient’s last follow-up consultation.

1. Endovascular treatment

Antiplatelet premedication was not routinely prescribed in the early study period. Most patients with unruptured aneurysms were pre-mediated with dual antiplatelet therapy (aspirin 100 mg, clopidogrel 75 mg once a day) for at least 5 days prior to the procedure according to the patients’ medical condition. But, we did not use prophylactic antiplatelet pre-medication for patients with acutely ruptured aneurysms.

SAH patients were treated within 24 hours after aneurysm rupture. In all patients with unruptured aneurysm, the therapeutic procedures were performed during a second angiography session. Local anesthesia was administered to all of the patients and electrocardiogram, arterial oxygen saturation, and blood pressure were appropriately monitored. A percutaneous intra-arterial approach was used after a standard Seldinger method and a 6 F introducer sheath was placed in the femoral artery. The baseline activated clotting time (ACT) was obtained before the procedure. Then patients received systemic heparinization and a bolus injection of 3,000 to 5,000 IU heparin just before starting the therapeutic procedure. A booster of 1,000 IU heparin was administered every hour to provide an ACT of longer than 250 seconds or twice the baseline ACT during the procedure.

A 6 F guiding catheter (Envoy; Cordis Endovascular, Miami Lakes, FL, USA) was positioned in the internal carotid artery (ICA). A 6 F Shuttle sheath was used in patients with tortuous aortic arch and carotid artery anatomy or in cases in which complex endovascular techniques were anticipated.

In most cases, coiling was tried first with the conventional single-catheter technique. When a single-catheter technique failed to make a stable coil mesh or was not suitable due to aneurysm geometry, aneurysm neck remodeling techniques using a multi-catheter, balloon, stent, or a combination of these were used.

Immediate angiographic results were classified according to the Raymond classification [13]. Complete occlusion was defined as occlusion of the entire aneurysm sac; neck remnant occlusion, as the minimal portion of the aneurysm neck region filled with contrast media; and incomplete occlusion, as the aneurysm dome filled with contrast media.

Immediate clinical outcome was evaluated according to the mRS by the neurosurgeons and the interventional neuroradiologist. All patients underwent non-enhanced brain computed tomography (CT) for evaluation of possible hemorrhagic complications and were monitored postoperatively at the intensive care unit.

After the procedure, 2,850 IU of low molecular weight heparin
(nadroparin) were also administered subcutaneously twice or three times a day for at least 2 days. The patients with stents were medicated dual antiplatelet therapy (aspirin 100 mg, clopidogrel 75 mg once a day) for at least 6 months.

2. Follow-up angiographic and clinical outcomes

Follow-up magnetic resonance angiography or DSA was performed 6 months after the procedure. To compare immediate and last follow-up angiographic results, we defined a three-grade scale using the Raymond classification scale [13] as follows: (1) stable or improved occlusion, (2) minor recanalization demonstrating a change from class 1 to class 2 at follow-up, requiring only additional follow-up imaging, and (3) major recanalization demonstrating a change from class 1 to class 3 or from class 2 to class 3 at follow-up, which required retreatment.

Follow-up clinical outcome was assessed by the neurosurgeons according to the mRS at last follow-up. Patients were classified as having favorable (mRS, 0–2) versus unfavorable outcomes (mRS, 3–6).

Results

Patient and aneurysm characteristics were summarized in Table 1. The 67 patients (40 women and 27 men) ranged in age from 23 to 82 years (mean, 58.8 years). Of the 72 MCA aneurysms, 38 were unruptured in 33 patients and 34 were ruptured in 34 patients. Five patients each had 2 MCA aneurysms at the opposite side. Of these, 1 patient presented with SAH. One unruptured aneurysm was a recurred aneurysm after coil embolization. Eight (11.1%) were located in the main trunk of the artery (M1 segment), 60 (83.3%) at the first major bifurcation, and only 4 at the distal of M2 (5.6%). Aneurysm diameters ranged 2–38.9 (mean, 6.8 mm) and aneurysm neck widths 1–11.9 (mean, 3.58 mm). HHGS in the ruptured group were grade I in 1, grade II in 7, grade III in 14, grade IV in 8, and grade V in 4 patients.

Three aneurysms were treated by the single-catheter technique. Sixty-nine aneurysms (95.8%) were treated with neck remodeling techniques using multi-catheter (n = 44, Fig. 1), balloon (n = 14, Fig. 2), stent (n = 8, Fig. 3), or combination of these (n = 3). Immediate post-embolization control angiograms revealed complete occlusion in 66, neck remnant occlusion in 5, and incomplete occlusion in 1 aneurysm by the Raymond classification.

In the 38 unruptured aneurysm patients, 37 aneurysms (97.4%) demonstrated complete occlusion and only 1 patient (2.6%) revealed residual neck. In contrast, the group of ruptured patients showed complete occlusion in 29 (85.3%), neck remnant in 4 (11.8%), and incomplete occlusion in 1 patient (2.9%).

Procedural complications occurred in 12 (16.7%) of 72 aneu-

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HHGS, Hunt and Hess grading scale; MCA, middle cerebral artery; M1, 1st segment of MCA; M2, 2nd segment of MCA.
Six of 38 unruptured aneurysms experienced complications, including procedural aneurysm rupture (n = 1) and acute thromboembolism without neurological deterioration (n = 5). Two of 5 acute thromboembolic patients experienced symptomatic acute stroke at 6 and 10 days after treatment. Six of 34 ruptured aneurysm patients experienced complications, including asymptomatic coil migration to the distal vessel (n = 1) and acute thromboembolism (n = 5) which consisted of 3 asymptomatic embolic infarctions and 2 symptomatic acute strokes.

One unruptured wide-necked aneurysm (5 mm in diameter) was ruptured during stent-assisted coil embolization. The M2 branch was occluded after temporary balloon occlusion of the distal M1 and additional coil embolization for bleeding control. The final angiogram revealed nearly complete occlusion of the aneurysm sac and no flow compromise. This patient had severe neurological deficits after embolization and SAH revealed on post-procedural CT. A follow-up CT the next day revealed SAH and severe brain swelling due to cerebral infarction requiring decompressive craniectomy. This patient experienced progressive infarction with hemorrhagic transformation and eventually died after 7 days.

Procedural coil migration occurred in one patient with a tiny
Fig. 2. A 73-year-old woman with a ruptured aneurysm at the left middle cerebral artery bifurcation. (A) Anteroposterior oblique view of left internal carotid angiogram shows an elongated aneurysm (arrows). (B) The aneurysm is treated with balloon-assisted technique (arrow) due to coil protrusion into the parent artery at coil insertion into the neck portion. Immediate post-procedural radiograph (C) and angiogram (D) reveal complete occlusion of the aneurysm (arrow) without coil protrusion into parent artery. Follow-up 18-month angiogram (E) and 41-month magnetic resonance angiogram (F) show stable, complete occlusion of the aneurysm (arrow).
Fig. 3. A 52-year-old man presented with severe headache. (A) Non-enhanced brain computed tomography reveals subarachnoid hemorrhage at the left Sylvian fissure. (B) Anteroposterior oblique view of left internal carotid angiogram shows a wide-necked aneurysm (arrow) at the left middle cerebral artery bifurcation and moderate to severe vasospasm of the anterior and middle cerebral arteries (arrowheads). (C) Prior to coil embolization, angioplasty using a compliant balloon (arrow) is performed to resolve vasospasm. The aneurysm is treated with a stent-assisted technique (arrows) and immediate post-procedural radiograph (D) and angiogram (E) reveal complete occlusion of the aneurysm (arrow) and restoration of vasospasm (arrowheads). (F) A 6-month follow-up angiogram after the procedure demonstrates stable complete occlusion of the aneurysm (arrow) and well-preserved parent artery.
ruptured aneurysm (2 mm in diameter) during a balloon-assisted embolization. The detached coil migrated into the distal M2 branch and on post-procedural angiogram, thrombotic occlusion was seen. After intra-arterial administration of a glycoprotein IIb/IIIa inhibitor (abciximab), acute thrombosis was lysed and the distal MCA flow was improved. At the immediate post-procedural neurological examination, patients did not show neurological differences compared to before the procedure; long-term follow-up DSA showed no flow compromise at the coil migrated distal MCA branch.

Acute thromboembolic complications occurred in 5 unruptured and 5 ruptured aneurysms in 10 patients. After intra-arterial administration of a glycoprotein IIb/IIIa inhibitor, acute thromboembolism was completely lysed in 9 patients, except for one patient with a ruptured aneurysm. One patient without recanalization after a glycoprotein IIb/IIIa inhibitor injection experienced major cerebral infarction and deterioration of consciousness level after the procedure and finally expired after 3 weeks. One patient with a ruptured aneurysm and recanalization after a glycoprotein IIb/IIIa inhibitor injection presented with progressive infarction within a day and was discharged at mRS2. Two of 5 acute thromboembolic patients with unruptured aneurysm presented with symptomatic acute stroke at 6 and 10 days after treatment even though no neurological deterioration was revealed on immediate post-procedural neurologic examination. The patients were discharged without neurologic deficit. But, the patients visited the emergency room for acute stroke and were discharged at mRS 1 and 4.

The rate of early post-procedural morbidity and mortality was 6.1% and 3.0% for unruptured aneurysms compared to 2.9% and 2.9% for ruptured aneurysms. As a result, over-all procedure-related permanent morbidity and mortality rates were 4.5% and 3.0% for unruptured and ruptured aneurysms, respectively. These data are summarized in Table 2.

In the final clinical grading of 33 unruptured aneurysm patients, 2 asymptomatic acute stroke patients were discharged at mRS 1 and 4 respectively. One patient improved to mRS 3. None of the surviving patients had any deterioration of functional neurological outcomes (mRS, 0-2).

Thirty-four patients with ruptured aneurysm were discharged with mRS 0 in 7 patients, mRS 1 in 10 patients, mRS 2 in 3 patients, mRS 3 in 2 patients, mRS 4 in 1 patient, mRS 5 in 4 pa-

Table 2. Endovascular treatment, complications, and angiographic and clinical outcomes

<table>
<thead>
<tr>
<th>Treatment methods, n (%)</th>
<th>Unruptured</th>
<th>Ruptured</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single catheter</td>
<td>1 (2.6)</td>
<td>2 (5.9)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Multicatheter</td>
<td>23 (60.5)</td>
<td>21 (61.8)</td>
<td>44 (61.1)</td>
</tr>
<tr>
<td>Balloon-assisted</td>
<td>8 (21.1)</td>
<td>6 (17.6)</td>
<td>14 (19.4)</td>
</tr>
<tr>
<td>Stent-assisted</td>
<td>4 (10.5)</td>
<td>4 (11.8)</td>
<td>8 (11.1)</td>
</tr>
<tr>
<td>Combined</td>
<td>2 (5.3)</td>
<td>1 (2.9)</td>
<td>3 (4.2)</td>
</tr>
</tbody>
</table>

| Procedure-related complications, n (%) | | |
|----------------------------------------| | |
| Coil migration                         | 1 (2.9) | 1 (1.4) |
| Thromboembolism                        | 5 (13.5) | 5 (14.3) | 10 (13.9) |
| Recanalization with ReoPro             | 5 (100) | 4 (80) | 9 (90) |
| Aneurysm rupture                       | 1 (2.7) | 1 (1.4) |

| Procedure-related permanent morbidity (%) | | |
|------------------------------------------| | |
| Favorable (mRS, 0-2)                     | 32 (97.0) | 20 (58.8) | 52 (77.6) |
| Unfavorable (mRS, 3-6)                   | 1 (3.0) | 14 (41.2) | 15 (22.4) |

| Immediate angiographic results, n (%)    | | |
|------------------------------------------| | |
| Complete                                 | 37 (97.4) | 29 (85.3) | 66 (91.7) |
| Neck remnant                             | 1 (2.6) | 4 (11.8) | 5 (6.9) |
| Incomplete                               | 1 (2.9) | 1 (1.4) |

| Follow-up angiographic results, n (%)    | | |
|------------------------------------------| | |
| Stable or improved                       | 18 (90.0) | 10 (83.3) | 28 (87.5) |
| Major recanalization                    | 1 (5.0) | 1 (3.1) |
| Minor recanalization                    | 1 (5.0) | 2 (16.7) | 3 (9.4) |

mRS, modified Rankin scale.
tients, and mRS 6 in 7 patients. Therefore, there were 20 patients in the favorable outcome group (mRS, 0–2) and 14 patients in the unfavorable outcome group (mRS, 3–6). Seven patients were hospitalized with HHGS IV or V and severe cerebral hemorrhage at the time of visit. They were mostly elderly and expired with severe cerebral hemorrhage and other systemic complications including pneumonia and multiple organ damage.

Clinical follow-up was available only in 12 of 34 ruptured patients because 22 patients were transferred to another hospital, died or outpatient visits were impossible. Thirty-two aneurysms in 31 of the 45 patients who could visit as outpatients at least once at 6–24 months (mean, 26 months; range, 6–96 months) received follow-up angiography. Follow-up angiographic results revealed 1 major and 3 minor recanalizations. One major recanalization aneurysm was re-treated by coiling with no complications.

**Discussion**

Ausman was the first neurosurgeon to advocate EVT of cerebral aneurysms as a first option treatment in 1997. In his experience, 50% of aneurysms were suitable for EVT [14]. Unlike coiling of other cerebral aneurysm locations, the success rate of MCA coiling was initially low at the beginning. In 1999, Regli et al. [2] reported on a consecutive series of 30 patients with 34 unruptured MCA aneurysms. Of the 34 aneurysms evaluated, only 2 (6%) were successfully obliterated with endovascular coil embolization. In 32% of the cases, EVT was attempted but abandoned, and in the remaining 62%, surgery was considered the best therapeutic choice. In this series, 94% of the unruptured MCA aneurysms were treated with surgical clipping. Until recently, EVT for MCA aneurysms showed a higher procedural failure rate and inconsistent results compared with EVT application to aneurysms at other sites [2,6-8,15,16].

MCA aneurysms have been traditionally considered not ideal for coiling because of their unfavorable anatomic features, including a wide neck and partial incorporation of 1 or both M2 branches [17]. Although the ISAT and some reports [18,19] have confirmed that EVT was equal or superior to clipping for all aneurysms regardless of their location, the treatment of MCA aneurysms, which accounted for 14% of aneurysms, is still controversial [20]. Recently, with the development of interventional devices and technologies, various neck remodeling endovascular techniques have attempted to treat MCA aneurysms with complex morphologic features. Even if EVT technology has advanced recently, neurovascular surgeons still seem to prefer clipping to coiling for MCA aneurysms. Suzuki et al. [15] reported a consecutive series of 115 patients with MCA aneurysms in which only 40% of patients were treated with coiling. Similarly, another recent study of 152 MCA aneurysms reported that 32.6% of the MCA aneurysms were either not considered for EVT or sent to surgery after EVT was attempted [16].

However, the selection rate for EVT of MCA aneurysms did not appear to be due to the difficulty of treating aneurysms via this technique. It seems that the difference is between medical institutions that consider MCA aneurysm embolization to be the first treatment modality and institutions that still believe surgery is the predominant treatment modality for MCA aneurysms. For example, there are some centers where embolization is the first treatment option considered [7,10]. In contrast, some institutions have applied very stringent criteria to select MCA aneurysm patients who will be treated with EVT. Raftopoulos et al. [4] chose EVT only when the ratio of neck to sac was less than 1:3. Our neurovascular team considered EVT as the first treatment modality for MCA aneurysms. Although almost all MCA aneurysms (95.8%) were treated with neck remodeling techniques, the technical success rate of EVT was 100% in this study. EVT for MCA aneurysms could be a technically feasible treatment strategy.

One major concern about EVT for MCA aneurysms is procedure-related complications. Choi et al. [21] compared the outcomes of clipping and coiling and evaluated the benefits of clipping for 178 ruptured and unruptured MCA aneurysms. Inclusion criteria for clipping were very strict and only 25 of 178 MCA aneurysms were treated by clipping. In their study, a multidisciplinary neurovascular team decided the treatment strategy (observation, clip, or coil) after discussion. If they expected there would be no definite benefits between the 2 treatment options (clip or coil) in terms of patient outcome and perioperative complications, they primarily chose microsurgical clipping. EVTs were considered in some selected cases that lacked complexity such as a relatively small neck (≤4 mm), large dome-to-neck ratio (>1.5), no incorporated branches in angiographic findings, clinically ruptured aneurysms with a high Hunt-Hess grade and/or use of medications such as warfarin. In the surgical group, perioperative complications occurred in 17 patients (11.1%). However, in the strictly selected EVT group, 8 patients (32%) experienced procedural complications (25% in the ruptured group and 35% in the unruptured group). Therefore, the complication rate for MCA embolization may seem to be high. However, most of the complications included 5 asymptomatic embolic infarctions observed on diffusion magnetic resonance (MR) imaging and 1 asymptomatic intraprocedural aneurysm rupture. Furthermore, there were no cases of procedure-related morbidity and mortality in the EVT group. Their results suggested that EVT for MCA aneurysms in selected patients can be effectively performed but the complica-

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tion rate is not negligible.

Generally, complications during EVT were stratified into three groups: (1) thromboembolic complications, (2) parent artery occlusion, and (3) aneurysm perforation [22]. But, it is not easy to analyze EVT complications compared to the complications of surgery. Because complications were determined by the neurointerventionalists who performed the procedure, there are many other factors that can or cannot be classified as complications.

The first reason is that EVT cases have not been analyzed yet and there are not enough to compare to clipping cases. The next reason is that the definition of EVT complications is vague and unclear. In the case of asymptomatic embolic infarction, institutions which perform MR diffusion after the procedure report it as a complication. But, it is not a complication at institutions that do not perform MR diffusion after the procedure.

In addition, aneurysm rupture during clipping is not classified as a complication. This is probably because most of them are controllable in the surgical field and do not cause other serious symptoms. Unlike clipping, aneurysm ruptures during embolization may cause serious symptoms and may lead to death or disability. However, many cases of intraprocedural rupture can be treated asymptptomatically. Therefore, it is unclear if asymptomatic rupture should be classified as a complication.

Most of the complications in this study were thromboembolism. We thought at first this was related to antiplatelet premedication. Thromboembolic complications occurred mainly in patients who did not receive premedication. In the early days of attempting unruptured MCA coiling, premedication was not administered.

The second cause of thromboembolism was related to selection criteria and the endovascular technique. We performed EVT as a first treatment for MCA aneurysms regardless of their morphological complexity. Most cases (95.8%) could by treated by neck-remodeling techniques using multiple catheters, balloon, or stent. These complex procedures using multiple intravascular devices were known to be a cause of thromboembolic complications [23].

Lastly, we performed the procedure with the goal of complete occlusion. Therefore, immediate angiographic outcomes revealed complete occlusion in 66 cases (91.7%) by the Raymond classification. Trying complete occlusion of an aneurysm may be likely to increase the incidence of thromboembolic complications during the procedure. Quadros et al. [7] prioritized prevention of thromboembolic complications during MCA aneurysm coiling. They did not treat with a complex, neck-remodeling technique in many cases and left the neck portion of the aneurysms to reduce the rate of thromboembolic complications.

Fortunately, thromboembolism could be prevented or resolved with administration of antiplatelet premedication or glycoprotein IIb/IIIa inhibitors. In this study, thromboembolism occurred in 10 patients. Although 2 patients experienced immediate post-procedural symptomatic ischemic events, procedural thromboembolism was completely lysed with intra-arterial administration of glycoprotein IIb/IIIa inhibitor. Therefore, like intraprocedural aneurysm rupture, it is unclear that the asymptomatic procedural thromboembolism should be classified as a complication.

Another major concern is the recurrence rate after coiling for MCA aneurysms [7]. Immediate angiographic complete occlusion was known to an important factor for decreasing recurrence rate after coiling [24]. Brinjikji at al. [22] reported in a review article of 12 series that post-operative complete occlusion was 82.4% and follow-up results of 758 aneurysms demonstrated that 70 (9.3%) had a minor recurrence not requiring re-treatment and 73 (9.6%) had major recanalization requiring retreatment. Overall angiographic stability or progression to better obliteration was reported in 81% of patients undergoing follow-up angiography. However, in our series, immediate angiographic outcomes were 91.7% complete occlusion; only 1 major recanalization (3.1%) was detected on follow-up angiography. We thought that this follow-up angiographic outcome might be related to complete occlusion immediately after the procedure.

There are some limitations in this study. First, this is a retrospective study and included a small number of MCA aneurysms cases at only 1 institution. Second is patient selection bias. As mentioned above, EVT is a first treatment option for MCA aneurysms in this study regardless of aneurysm morphological complexity. Considering improved operator experience and devices, our result may not represent the general situation of MCA coiling in this era because our cases were collected over 10 years.

Coil embolization of MCA aneurysms could be a technically feasible and clinically effective treatment strategy with acceptable angiographic and clinical outcomes. In the future, increased operator experience, improved new devices, and various neck-remodeling techniques might greatly increase the feasibility and efficacy of MCA aneurysm coiling.

However, the safety and efficacy of this technique as compared to surgical clipping remains to be determined.

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Conflicts of interest

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

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References


Factors that determine the Work Ability Index of street cleaners

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Introduction

According to the Korea National Statistical Office, most street cleaners are over 50 years old; the mean age of street cleaners is 58.4 years, which is higher than the average ages of other workers—for instance, 50.4 years for managers, 38.5 years for professional workers, 39.6 years for office workers, 45.5 years for service workers, 39.1 years for sales workers, and 44.0 years for agricultural workers [1]. As of August 2018, the labor force participation rate of the elderly is 69.1%, and the employment rate of the elderly is 66.9% [2]. It is therefore important that middle-aged workers be able to maintain their health in the industrial setting and exercise their maximum work ability.

Work ability is the ability to carry out a given job well and to maintain physical and mental health. In Europe, a number of studies have indicated that increasing age reduces working ability [3-5]. Decreases in the youth population due to aging and increases in the mean age of the workforce are associated with re-
duced work productivity owing to reduced working ability [6]. As workers age, disability and illness increase due to reduced working ability and declining physical and mental abilities [7]. According to the U.S. Bureau of Labor Statistics, the number of major accidents among street cleaners in 2016 was 5.7 per 1,000 workers, with 439 being industrial accidents, making it the fourth most dangerous job in the US [8].

Working ability largely involves power of the muscles and respiratory system to determine how much work can be done in a given amount of time and how long one can last at the same strength. Therefore, we used maximal oxygen consumption (VO\(_{2\text{max}}\)) as an indicator of aerobic work ability. VO\(_{2\text{max}}\) is highly correlated with total endurance including cardiopulmonary ability, oxygen transport ability of the blood, and oxygen utilization ability of tissues [9].

In addition to age and aerobic work ability, work performance, body mass index, personal health status, and psychosocial stress have been reported to affect Work Ability Index (WAI) [10-13]. The relationship between age and WAI is controversial. While there are studies reporting negative correlations between age and WAI due to decreased physical ability, cognitive ability, and reaction rates in elderly people, there is also a study reporting a positive correlation owing to increasing work proficiency [10]. Additionally, there are studies reporting no correlation between age and WAI [13].

A few reports indicate other factors affecting the WAI besides psychosocial stress, age, work type, and aerobic work ability, and there are also a few regarding drinking habits and WAI. Therefore, it is important to understand the relationship between age and WAI and to identify other factors that affect WAI, including drinking habits.

The purpose of this study was to identify the factors affecting the WAI of street cleaners and to use these data for the evaluation and management of working ability among middle-aged workers in the future.

Materials and methods

The study population comprised 411 street cleaners who visited occupational health facilities in Daegu from 2015 to 2017. Of these, 371 people were included in the final study population after excluding 28 cases including a small percentage of female cases, 10 cases of individuals with existing cerebral cardiovascular disease or pulmonary disease, and two cases of incomplete responses to the questionnaire.

Body fat and skeletal muscle percentage rate were measured using an Inbody 770 (InBody Korea [HQ], Seoul, Korea). The Alcohol Use Disorders Identification Test-Korea (AUDIT-K) was conducted with scores ranging from 0 to 27. Higher scores indicated a higher risk of a drinking habit. Drinking status was categorized as "low" if the score was below 11 and otherwise "high" [14]. The Psychosocial Well-Being Index-Short Form (PWI-SF) questionnaire was used to assess psychosocial stress on a 4-point scale; each item was assigned a score of 0-1-2-3 and the scores were added up. On a scale of 0 to 54, scores lower than 27 were classified as "low," meaning low stress, and higher scores were classified as "high" [15].

Work ability was assessed using the WAI questionnaire. The WAI questionnaire [16]: consists of seven items on physical, mental, and social competence. Each item has a range of 0 to 10, and on item 1, current work ability is measured on a 10-point scale as compared to most active work ability. On item 2, physical and mental conditions related to job performance are measured on a 5-point scale. The weight for each item is given differently depending on whether the worker has a blue-collar or white-collar occupation. On item 3, a score is given based on the number of diseases diagnosed by a doctor (1 point for more than 5 diseases, 7 points for no disease). On item 4, the degree of occupational disability due to disease is measured on a 6-point scale. Item 5 is measured on a 5-point scale assessing the number of days of absence or illness, and item 6 is measured on a 7-point scale measuring the extent to which the respondent expects to be able to continue working after 2 years. On item 7, the mental health status of workers is further divided and the results are summed to obtain a score. The total score is evaluated from a minimum of 7 points to a maximum of 49 points.

The VO\(_{2\text{max}}\) was calculated using the Bruce equation (85.42–13.73×sex–0.409×age [yr]) –3.24–0.114×weight (kg).

In this study, an independent t-test and a correlation test were performed to investigate the variables that affect WAI. The adjustment variables, which showed p-values ≤ 0.2 in the univariate analysis, were included in the multiple logistic regression as independent variables. WAI was the dependent variable. All statistical analyses were performed using IBM SPSS version 25.0 (IBM Co., Armonk, NY, USA). This study was approved by the Institutional Review Board of Keimyung University Hospital (2019-03-047-001).

Results

The ages of the 371 subjects ranged from 21 to 70 years, and the mean age was 48.6 years (Table 1). There was a statistically significant negative correlation between age and WAI (Table 2). As age increased, WAI tended to decrease (Table 3).
Table 1. Characteristics of study subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>371</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>204 (55.0)</td>
</tr>
<tr>
<td>≥50</td>
<td>167 (45.0)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.7±10.7</td>
</tr>
<tr>
<td>BMI</td>
<td>24.7±3.1</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>20.8±6.2</td>
</tr>
<tr>
<td>Percent skeletal muscle (%)</td>
<td>31.8±4.4</td>
</tr>
<tr>
<td>V02max</td>
<td>40.4±4.1</td>
</tr>
<tr>
<td>AUDIT-K</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>251 (67.7)</td>
</tr>
<tr>
<td>High</td>
<td>120 (32.3)</td>
</tr>
<tr>
<td>PWI-SF</td>
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</tr>
<tr>
<td>Low</td>
<td>339 (91.4)</td>
</tr>
<tr>
<td>High</td>
<td>32 (8.6)</td>
</tr>
<tr>
<td>Smoking</td>
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<tr>
<td>No or ex</td>
<td>218 (58.8)</td>
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<tr>
<td>Current</td>
<td>153 (41.2)</td>
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<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
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<tr>
<td>Yes</td>
<td>27 (7.3)</td>
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<td>344 (92.7)</td>
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<td>Diabetes mellitus</td>
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<td>17 (4.6)</td>
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<tr>
<td>Hyperlipidemia</td>
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</tr>
<tr>
<td>Yes</td>
<td>13 (3.5)</td>
</tr>
<tr>
<td>No</td>
<td>358 (96.5)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%). BMI, body mass index; V02max, maximal oxygen consumption; AUDIT-K, Alcohol Use Disorders Identification Test-Korea; PWI-SF, Psychosocial Well-Being Index-Short form.

Mean height was 170.3 cm and mean weight was 71.7 kg. There was no statistically significant correlation between height and WAI or between weight and WAI (p = 0.173, p = 0.123). The mean body mass index (BMI) was 24.7, and there was a statistically significant negative correlation (p = 0.007) between BMI and WAI. The mean body fat percentage was 20.8%. There was a statistically significant negative correlation (p = 0.001) between percent body fat and WAI. There was a statistically significant positive correlation (p < 0.001) between VO2max and WAI. When comparing AUDIT-K scores results, the low group included 251 participants (67.7%) while the high group included 120 (32.3%); there was a statistically significant difference (p < 0.001). When comparing PWI-SF scores results, there was a statistically significant difference (p = 0.002) with the low group including 339 (91.4%) participants, while the high group included 32 (8.6%). Additionally, 27 cases (7.3%) were taking antihypertensive medication, and there was a statistically significant difference in WAI scores between the antihypertensive medication group and the non-medication group (p = 0.035). In addition, there was no statistically significant difference between the two groups in terms of skeletal muscle percentage, smoking status, diabetes medication history, and hyperlipidemia medication history (Table 4).

The adjustment variables included in the multiple linear regression analysis were age, BMI, percent body fat, AUDIT-K scores, PWI-SF scores, and hypertension; these were included in the analysis because the p-values were ≤ 0.2. In the stepwise linear multiple regression analysis with WAI and seven independent variables, VO2max, AUDIT-K scores, and PWI-SF scores were significant at a significance level of 0.05; age, BMI, and body fat percentage were not significant. The VO2max, AUDIT-K scores, and PWI-SF scores accounted for 11.8% of the total variation. VO2max had the greatest effect, followed by the AUDIT-K scores and PWI-SF scores results (Table 5).
Discussion

In this study, WAI was used to evaluate working ability. WAI was developed at the Finnish Institute of Occupational Health in Finland in 1994 for the purpose of assessing the working ability of older workers [16]. Factors influencing WAI include lack of leisure time, excessive workload, musculoskeletal abilities, age, obesity, lack of autonomy, and need of high physical abilities [17].

There has been much research on the relationship between age and WAI, but the findings are contradictory. Lee and Chang [10] reported that working ability and age were not linear; working ability seemed high in the early 20s and 30s age ranges but gradually decreased from the late 30s, and it was highest above 55 years due to proficiency. However, Bridger and Bennett [11] and Bugajska et al. [18] reported negative correlations. In this study, age and WAI seemed to be negatively correlated, which means that WAI decreases as age increases. Studies have reported negative correlations between age and WAI due to decreased physical ability, cognitive ability, and reaction rates among elderly people. However, other studies have reported positive correlations due to increased work proficiency.

In the present study, VO$_{2\text{max}}$ was the most influential factor for WAI. In the regression equation of this study, the standardization factor of VO$_{2\text{max}}$ was 0.239; as VO$_{2\text{max}}$ increased, WAI also increased. As aerobic work ability increased, working ability also increased. Bugajska et al. [18] reported a positive correlation between VO$_{2\text{max}}$ and WAI among 524 Polish women and 664 Polish male workers. However, Habibi et al. [19] reported no statistical significance between the two variables among 228 Iranian nurses. As working ability is affected by physical conditions, the higher the VO$_{2\text{max}}$, which indicates aerobic work ability, the greater the working ability. In particular, street cleaners show a large
correlation between $VO_{2\text{max}}$ and WAI because they engage in many outdoor activities.

The standardization factor of the AUDIT-K scores was -0.178, and the standardization factor of the PWI-SF scores was -0.151. In this study, the groups with good drinking habits and low psychosocial stress had great working ability. Hur et al. [15] reported that there was no statistically significant relationship between drinking habits and work ability, but reported that working ability decreased with increasing psychosocial stress. Ye et al. [20] reported that the higher the level of psychosocial stress, the lower the working ability. Kim and Kim [13] and Lee et al. [14] also reported that stress and WAI were negatively correlated. It is suggested that stress management is helpful for improving work ability. The relationship between drinking habits and working ability were unknown in previous studies. In the present study, the group with good drinking habits showed higher WAI. Alcohol weakens attentiveness, motor coordination abilities, and response speed to external stimuli; thus, post-drinking tasks show reduced job accuracy and efficiency. There is also the possibility of reducing working ability by increasing impulsive behavior and weakening temperance. Therefore, proper drinking habits should improve work ability.

In this study we used the WAI, which can visually evaluate the abstract concept of working ability, to increase the reliability of the study. Age and also body fat percentage, alcohol status, and psychosocial stress were included as independent factors.

The present study has several limitations. It is difficult to generalize the findings because it investigated mostly male street cleaners in only one area. Factors such as job stress or shift work may also affect work ability, but these factors are not reflected. In addition, there is a limitation in that $VO_{2\text{max}}$ cannot be obtained directly but was estimated using an indirect formula.

The significant findings of this study showed that aerobic physical ability, drinking habits, and psychosocial stress were correlated with working ability. Experimental evaluation of working ability, such as oxygen consumption and maximum heart rate, has the advantage of obtaining accurate results under constrained conditions, but it is difficult to apply at the worksite, and there are also time and cost constraints. On the other hand, work performance evaluation using the WAI questionnaire is subjective. Reliability is not high compared with the experiment, but this evaluation method is simple, time and cost effective, and easy to apply at the actual work site. Therefore, middle-aged workers will be able to utilize WAI as an indicator of their working ability in programs that can then easily evaluate and maintain their physical ability.

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**Conflicts of interest**

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

**References**


Computer-based clinical coding activity analysis for neurosurgical terms

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Background: It is not possible to measure how much activity is required to understand and code a medical data. We introduce an assessment method in clinical coding, and applied this method to neurosurgical terms.

Methods: Coding activity consists of two stages. At first, the coders need to understand a presented medical term (informational activity). The second coding stage is about a navigating terminology browser to find a code that matches the concept (code-matching activity). Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT) was used for the coding system. A new computer application to record the trajectory of the computer mouse and record the usage time was programmed. Using this application, we measured the time that was spent. A senior neurosurgeon who has studied SNOMED CT has analyzed the accuracy of the input coding. This method was tested by five neurosurgical residents (NSRs) and five medical record administrators (MRAs), and 20 neurosurgical terms were used.

Results: The mean accuracy of the NSR group was 89.33%, and the mean accuracy of the MRA group was 80% (p=0.024). The mean duration for total coding of the NSR group was 158.47 seconds, and the mean duration for total coding of the MRA group was 271.75 seconds (p=0.003).

Conclusion: We proposed a method to analyze the clinical coding process. Through this method, it was possible to accurately calculate the time required for the coding. In neurosurgical terms, NSRs had shorter time to complete the coding and higher accuracy than MRAs.

Keywords: Clinical coding; Medical informatics; Systematized nomenclature of medicine

Introduction

Recently, the ability to collect and analyze data has developed, and researches using so-called “big data” have been actively conducted in various fields [1]. In the medical area, various studies using big data also have been attempted. However, differences in clinical coding systems and data structures are major barriers to such researches [2]. Therefore, researches on data standardization using a tool such as a common data model is being carried out [3]. In our country, researches on standardizing medical data are also conducted by the government [2].

However, maintaining such standardized medical data requires human and financial resources in hospitals, and there have been challenges regarding accuracy, coding variation, quality assurance and so on [4-6]. Recently, the adoption and use of electronic health records (EHRs) system has been increasing worldwide.
Thus, it has become easier to collect medical data. However, most EHRs are not interchangeable [7]. In the neurosurgical fields, the incidence of diseases is relatively low, and there are many surgical techniques that have relatively low frequency. Thus, medical data before EHRs is also very important in the neurosurgical field. It is not possible to measure how much activity is required for individuals to understand a medical data objectively or how much time is needed to search codes when they already know the meaning of medical data. Such information will be very important in predicting the costs of future research. We will also be able to identify problems with clinical coding. The purpose of this study is to propose a clinical coding activity analysis method using the computer mouse, and to analyze the results after coding of neurosurgical terms using this method.

Material and methods

1. Collection of neurosurgical data
We selected 1,071 patients who was admitted to the neurosurgical department for a year at our institute. We reviewed the name of the surgery and the diagnosis. From this pool of terms, we randomly selected 10 names of the diagnosis and 10 names of the surgery using "Rand function" of Microsoft Office Excel 2013 (Microsoft Co., Redmond, WA, USA). Selected terms are listed in Table 1.

2. Systematized Nomenclature of Medicine – Clinical Terms
The Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT) is an international clinical terminology that can facilitate interoperability by capturing clinical data in a standardized manner. The International Health Terminology Standards Development Organization was established to maintain and promote SNOMED CT as a clinical reference terminology. Many countries have designated SNOMED CT as the preferred clinical reference terminology for use in EHRs [8]. However, it is not used in our country. We used SNOMED CT, which coders participating in this study have never used.

3. Clinical coding activity
In this study, clinical coding activity consists of two stages. In the first stage, the coders need to understand a presented medical term (informational activity). They use the internet search engine to understand the meaning of terms or abbreviations during information activity. The second stage is about navigating the terminology browser to find a code that matches the concept (code-matching activity). In order to evaluate the accuracy of these activities, a senior neurosurgeon who has studied SNOMED CT has analyzed the accuracy of input coding.

This coding activity was carried out by five neurosurgical residents (NSRs) as domain experts and five medical record administrators (MRAs) as coding experts. The NSRs consisted of two fourth-year residents, two third-year residents, and a second-year resident. And, the career of MRAs was at least 5 years. However, both of the groups had very limited experience with SNOMED CT and CliniClueXplore, which was used as the browser of SNOMED CT. Before the experiment, we briefly gave instruction on how to use CliniClueXplore and SNOMED CT in general to each test subject. The time required for introduction was about 20 minutes. During the test, there was no more explanation or instruction for understanding the meaning of given terms. The randomly collected diagnosis and surgery terms were presented to each participant to perform the clinical coding activity.

Table 1. The list of randomly selected neurosurgical diagnosis and surgery names

<table>
<thead>
<tr>
<th>No</th>
<th>Diagnosis name</th>
<th>No</th>
<th>Surgery name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Spinal stenosis with foraminal stenosis L4/5 L5/S1</td>
<td>11</td>
<td>Nerve root block L2 Lt</td>
</tr>
<tr>
<td>2</td>
<td>HNP L4/5 Lt sequestrated</td>
<td>12</td>
<td>OLM L4/5 Rt</td>
</tr>
<tr>
<td>3</td>
<td>Brain tumor (R/O atypical meningioma)</td>
<td>13</td>
<td>ACFD C4/5 with allogenic bone filled zero-p PEEK cage</td>
</tr>
<tr>
<td>4</td>
<td>Unruptured aneurysm MCA aneurysm</td>
<td>14</td>
<td>Clipping of aneurysm</td>
</tr>
<tr>
<td>5</td>
<td>Hydrocephalus</td>
<td>15</td>
<td>Osteoplastic craniotomy for removal of acute SDH Lt F-T-P</td>
</tr>
<tr>
<td>6</td>
<td>Fracture of odontoid process (Type II)</td>
<td>16</td>
<td>Transcorporeal approach C6/7 Rt</td>
</tr>
<tr>
<td>7</td>
<td>Mature teratoma at middle cranial fossa with extracranial extension</td>
<td>17</td>
<td>Transsylvian approach for removal of ICH Rt basal ganglia</td>
</tr>
<tr>
<td>8</td>
<td>Posthemorrhage hydrocephalus</td>
<td>18</td>
<td>Percutaneous endoscopic laminectomy</td>
</tr>
<tr>
<td>9</td>
<td>Spinal intradural tumor T9/10 Rt (R/O Schwannoma)</td>
<td>19</td>
<td>UBL L3/4 Rt</td>
</tr>
<tr>
<td>10</td>
<td>Suprasellar cystic tumor with optic neuropathy</td>
<td>20</td>
<td>IPG insertion</td>
</tr>
</tbody>
</table>

HNP, herniated nucleus pulposus; Lt, left; R/O, rule out; MCA, middle cerebral artery; Rt, right; OLM, open laminectomy and microdisectomy; ACFD, anterior cervical decompression and fusion; PEEK, polyetheretherketone; SDH, subdural hematoma; F-T-P, frontotemporoparietal; ICH, intracerebral hematoma; UBL, unilateral approach and bilateral laminectomy; IPG, implanted pulse generator.
4. Computer-based clinical coding activity analysis

The user’s computer-based clinical coding activity analysis (CBC-CAA) was implemented as follows. A computer application to record the trajectory of the computer mouse and record the usage time was programmed. And user interface was built with Microsoft Office Access 2007 (Microsoft Co.), which could store terms and codes. On the first page of the question window, simple instructions for the experiment and input fields for demographic information were placed. When the participants clicked the ‘Start’ button, first term could be seen and the participants could enter SNOMED CT codes into the textbox of the question window (Fig. 1). At the same time, our program would start measuring the time that was spent on each activity. When the participant clicked the ‘Next’ button, the next term was presented, and the time taken for each individual term was recorded.

With this set up, we measured the length of each user’s computer activity with our application. As we used two computer monitors to capture mouse movements, the participant could keep the SNOMED CT browser at maximum size at all times, so that we could easily analyze each user’s activity on each browser (Fig. 2). The computer activity was decided by the location of mouse clicks and wheel events. If those mouse activities were developed in the web browser, the length of the activity was assigned into the informational activity, because the user’s intention was trying to understand the meaning of a given term using web browsing. Meanwhile, the code-matching activity would be the length of clicking and wheel events on the SNOMED CT browser.

5. Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Clinical coding activity was compared using an independent t-test. Probability values of less than 0.05 were considered to be statistically significant.

Results

All coding activities analyzed are listed in Table 2. In the NSR group, the most inaccurate term for coding was term 1 (spinal ste-
nosis with foraminal stenosis L4/5 L5/S1), and the most time-consuming term for coding activity was term 16 (transcorporeal approach C6/7 right [Rt]). On the other hands, in the MRA group, the most inaccurate term for coding was term 16 (transcorporeal approach C6/7 Rt) and term 20 (implanted pulse generator insertion), and the most time-consuming term for coding activity was term 7 (mature teratoma at middle cranial fossa with extracranial extension). The accuracy and total coding time were inversely proportional (Pearson’s correlation coefficient = –0.438, p-value = 0.005).

The CBCCAA illustrated the characteristics of two coder groups. The accuracy of coding activity in the NSR group is higher than the MRA group (p = 0.024). The mean duration of informational activity (p < 0.001) and total duration of coding activity (p = 0.003) in the NSR group was shorter than the MRA group. The mean duration of code-matching activity in the NSR group was also shorter than the MRA group, but there was no statistical significance (p = 0.07) (Table 3). In the NSR group, the informational stage was significantly shorter than code-matching stage, but there was no statistical significance in the MRA group (Table 4).

Analysis of coding activity according to diagnosis versus surgery name was performed, but there was no statistically significant difference. Coding according to subspecialties of neurosurgical disorders was also analyzed. In both brain and spine part, the mean duration of informational activity and total duration of coding activity in the NSR group was shorter than the MRA group (Table 5).

### Table 2. All data of coding activity in both coder groups

<table>
<thead>
<tr>
<th>Term</th>
<th>NSR</th>
<th>MRA</th>
<th>NSR</th>
<th>MRA</th>
<th>NSR</th>
<th>MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60.00</td>
<td>80.00</td>
<td>88.24</td>
<td>143.81</td>
<td>181.45</td>
<td>208.93</td>
</tr>
<tr>
<td>2</td>
<td>93.33</td>
<td>73.33</td>
<td>47.18</td>
<td>108.00</td>
<td>132.99</td>
<td>204.38</td>
</tr>
<tr>
<td>3</td>
<td>73.33</td>
<td>86.67</td>
<td>46.51</td>
<td>43.09</td>
<td>46.48</td>
<td>81.10</td>
</tr>
<tr>
<td>4</td>
<td>93.33</td>
<td>100.00</td>
<td>23.54</td>
<td>84.85</td>
<td>120.15</td>
<td>126.49</td>
</tr>
<tr>
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<td>100.00</td>
<td>100.00</td>
<td>38.12</td>
<td>102.91</td>
<td>147.25</td>
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<td>6</td>
<td>93.33</td>
<td>86.67</td>
<td>52.07</td>
<td>81.67</td>
<td>62.90</td>
<td>66.37</td>
</tr>
<tr>
<td>7</td>
<td>86.67</td>
<td>93.33</td>
<td>37.79</td>
<td>153.60</td>
<td>118.49</td>
<td>390.21</td>
</tr>
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<td>8</td>
<td>100.00</td>
<td>100.00</td>
<td>12.70</td>
<td>19.63</td>
<td>18.04</td>
<td>43.27</td>
</tr>
<tr>
<td>9</td>
<td>93.33</td>
<td>80.00</td>
<td>38.58</td>
<td>137.96</td>
<td>178.43</td>
<td>239.24</td>
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<td>10</td>
<td>86.67</td>
<td>66.67</td>
<td>32.29</td>
<td>78.35</td>
<td>98.17</td>
<td>140.54</td>
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<td>11</td>
<td>100.00</td>
<td>86.67</td>
<td>30.10</td>
<td>26.19</td>
<td>82.20</td>
<td>72.54</td>
</tr>
<tr>
<td>12</td>
<td>100.00</td>
<td>80.00</td>
<td>30.24</td>
<td>107.93</td>
<td>98.95</td>
<td>118.11</td>
</tr>
<tr>
<td>13</td>
<td>93.33</td>
<td>80.00</td>
<td>30.84</td>
<td>192.09</td>
<td>210.81</td>
<td>134.66</td>
</tr>
<tr>
<td>14</td>
<td>80.00</td>
<td>80.00</td>
<td>6.33</td>
<td>17.28</td>
<td>14.34</td>
<td>34.30</td>
</tr>
<tr>
<td>15</td>
<td>93.33</td>
<td>66.67</td>
<td>34.78</td>
<td>157.47</td>
<td>119.56</td>
<td>293.81</td>
</tr>
<tr>
<td>16</td>
<td>80.00</td>
<td>53.33</td>
<td>132.45</td>
<td>202.61</td>
<td>142.45</td>
<td>191.48</td>
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<tr>
<td>17</td>
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<td>80.00</td>
<td>31.76</td>
<td>153.60</td>
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<td>285.84</td>
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<tr>
<td>18</td>
<td>93.33</td>
<td>93.33</td>
<td>19.40</td>
<td>52.64</td>
<td>85.81</td>
<td>105.63</td>
</tr>
<tr>
<td>19</td>
<td>86.67</td>
<td>60.00</td>
<td>67.57</td>
<td>225.79</td>
<td>105.48</td>
<td>137.05</td>
</tr>
<tr>
<td>20</td>
<td>80.00</td>
<td>53.33</td>
<td>108.31</td>
<td>190.18</td>
<td>110.67</td>
<td>100.71</td>
</tr>
</tbody>
</table>

All values are mean.
NSR, neurosurgical resident; MRA, medical record administrator.

### Table 3. Comparison of coding parameters between two coder groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NSR</th>
<th>MRA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy (%)</td>
<td>89.33±10.46</td>
<td>80.00±14.35</td>
<td>0.024</td>
</tr>
<tr>
<td>Informational stage (s)</td>
<td>45.44±31.59</td>
<td>113.99±63.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Code-matching stage (s)</td>
<td>113.03±53.45</td>
<td>157.76±92.24</td>
<td>0.070</td>
</tr>
<tr>
<td>Total time for coding (s)</td>
<td>158.47±70.03</td>
<td>271.75±137.85</td>
<td>0.003</td>
</tr>
</tbody>
</table>

NSR, neurosurgical resident; MRA, medical record administrator.
Table 4. Comparison of coding activities between information and code-matching stages

<table>
<thead>
<tr>
<th>Coder group</th>
<th>Informational stage (s)</th>
<th>Code-matching stage (s)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSR</td>
<td>45.44±31.59</td>
<td>113.03±53.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRA</td>
<td>113.99±63.61</td>
<td>157.76±92.24</td>
<td>0.089</td>
</tr>
</tbody>
</table>

NSR, neurosurgical resident; MRA, medical record administrator.

Table 5. Comparison of coding activities between spine and brain part

<table>
<thead>
<tr>
<th></th>
<th>Brain</th>
<th>Spine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NSR</td>
<td>MRA</td>
<td>p-value</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>89.33±9.53</td>
<td>82.67±16.39</td>
<td>0.281</td>
</tr>
<tr>
<td>Informational stage (s)</td>
<td>37.21±27.78</td>
<td>100.1±61.86</td>
<td>0.012</td>
</tr>
<tr>
<td>Code-matching stage (s)</td>
<td>97.92±55.53</td>
<td>167.68±118.90</td>
<td>0.117</td>
</tr>
<tr>
<td>Total time for coding (s)</td>
<td>135.13±69.18</td>
<td>267.79±168.34</td>
<td>0.040</td>
</tr>
</tbody>
</table>

NSR, neurosurgical resident; MRA, medical record administrator.

Discussion

Recently, as interest in big data, deep learning, and artificial intelligence has increased, interest in data collection has increased. In order to receive compensation, the code related to the health insurance had to be continuously input, and many studies using this data have been performed [9]. However, such data are limited, and new data collection is required depending on the content of the study. For clinical data collection and standardization, coding the data at each hospital is very important. Understanding and code-searching are the two main stages of medical coding. We tried to use these two particular concepts to analyze clinical coding activity.

In this study, we provided a method to evaluate coding activity in an objective way. A benefit of this method is that the parameters are produced with numeric values that can be measured by computers. Thus, we can compare parametric results quantitatively, and can analyze the efficiency according to the coder and kind of terminology. When we reviewed the data in this study, coding activities were very varied greatly, depending on the coders. The NRS group did more efficient coding than the MRA group. The coding time was significantly shorter in the information stage, and thus the total time was shortened (Table 3). The accuracy of coding was higher in NSR group, probably because they understood neurosurgical terms better than the MRAs did. We expected that the MRA group would take less time for code-matching, because they specialized in coding. However, there was no significant difference in the code-matching time between the NSR group and the MRA group. In the healthcare field, there are various type of occupations (physicians, dentist, nurses, MRA, clinical laboratory technologists, radiologic technologists, etc.) and costs are different. Using the method presented in this study, it can be expected which job group will be efficiently at clinical coding data.

We also analyzed coding processes by each stages. In the NSR group, the informational stage was shorter than code-matching stage. As mentioned previously, a short informational activity means that the coder has no difficulty with understanding the terms. On the other hands, long code-matching activity refers to problems matching concepts to codes in the terminology browser. Inefficient browsers can be more time-consuming in code-matching activity. Thus, if this phenomenon persists, the browser used for coding should be improved. We also analyzed the coding activity according to the kind of terminology. Neurosurgical diseases and surgery were classified into brain and spine. In both brain and spine part, coding activity of the NSR group was effective than the MRA group.

In this study, we can confirm that the coding time was longer for terms that had low coding accuracy, because less-understood terms took longer to find. For example, a term that was difficult to code in both groups was “transcorporeal approach C6/7, Rt,” because this is that this surgery has been proposed relatively recently, and is called by various names [10].

Although the coders could start the test by pressing a button, the coder’s activity was measured by the length of activity on the designated window. Because the computer mouse logging function automatically evaluates the coding process, there is no manual evaluation to categorize the coder’s activity which may lead to subjective results. Since we are heading towards a computerized coding environment, those parameters need to be evaluated by computer-based tools as well [11]. As far as we know, this is the first study to analyze the clinical coding process by means of computer activity. By this approach, we can clarify practical problems.
with coding activity and analyze proper solutions to such issues.

**Conflicts of interest**

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

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**References**


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Assessment of solid components of borderline ovarian tumor and stage I carcinoma: added value of combined diffusion- and perfusion-weighted magnetic resonance imaging

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Background: We sought to determine the value of combining diffusion-weighted (DW) and perfusion-weighted (PW) sequences with a conventional magnetic resonance (MR) sequence to assess solid components of borderline ovarian tumors (BOTs) and stage I carcinomas.

Methods: Conventional, DW, and PW sequences in the tumor imaging studies of 70 patients (BOTs, n=38; stage I carcinomas, n=32) who underwent surgery with pathologic correlation were assessed. Two independent radiologists calculated the parameters apparent diffusion coefficient (ADC), $K_{trans}$ (vessel permeability), and $V_{c}$ (cell density) for the solid components. The distribution on conventional MR sequence and mean, standard deviation, and 95% confidence interval of each DW and PW parameter were calculated. The inter-observer agreement among the two radiologists was assessed. Area under the receiver operating characteristic curve (AUC) and multivariate logistic regression were performed to compare the effectiveness of DW and PW sequences for average values and to characterize the diagnostic performance of combined DW and PW sequences.

Results: There were excellent agreements for DW and PW parameters between radiologists. The distributions of ADC, $K_{trans}$, and $V_{c}$ values were significantly different between BOTs and stage I carcinomas, yielding AUCs of 0.58 and 0.68, 0.78 and 0.82, and 0.70 and 0.72, respectively, with ADC yielding the lowest diagnostic performance. The AUCs of the DW, PW, and combined PW and DW sequences were 0.71±0.05, 0.80±0.05, and 0.85±0.05, respectively.

Conclusion: Combining PW and DW sequences to a conventional sequence potentially improves the diagnostic accuracy in the differentiation of BOTs and stage I carcinomas.

Keywords: Borderline ovarian tumor; Diagnosis; Magnetic resonance imaging; Stage I ovarian carcinoma

Introduction

The presence of solid components in ovarian tumors strongly suggests carcinoma, but solid components can also be seen in borderline ovarian tumors (BOTs). BOTs are a class of epithelial tumors; histologically, they show atypical nuclei without cell proliferation and epileptic involvement. Resection is considered to be sufficient treatment for BOTs; adjuvant chemotherapy after...
Materials and methods

This study was approved by the Kyungpook National University Hospital Institutional Review Board (Approval No. S-201221) with waiver of informed consent. We reviewed the medical records dating from December 2015 to May 2017 of 118 patients with BOTs or stage I carcinomas treated in our institution. Of these patients, 70 with solid tumors on MRI were included (BOTs, 38 patients; stage I carcinomas, 32 patients). All tumor diagnoses were confirmed histopathologically. MRI, including conventional, DW, and PW sequences, was performed in 57 of the 70 patients. DW sequences were excluded in 7 patients (T1-weighted high-intensity mass, 3 patients; artifact shadow, 4 patients), and 9 patients (contrasted myometrial defects, 4 patients; technical problems such as artificial shadowing, 5 patients). Table 1 summarizes the results of the exponential test in the patient groups that underwent imaging with DW and PW sequences in combination with conventional MRI. Of the patients with tumors identified as BOTs, 12 had mucinous tumors and 26 had serous tumors, whereas 11 of the patients with stage I carcinoma had mucinous tumors and 21 had serous tumors. The ages of the patients with BOTs ranged from 19 to 62 years (mean, 40.8 ± 14.2 years). The ages of the patients with stage I carcinoma ranged from 25 to 71 years (mean, 43.2 ± 13.2 years). Thirteen patients had undergone unilateral or bilateral salpingo-oophorectomy (BSO) due to clinical conditions such as fertility problems. The remaining patients had undergone hysterectomy, BSO, and lymphadenectomy for a clinical diagnosis of carcinoma.

MRI was performed with a 1.5-T scanner (Avanto; Siemens, Erlangen, Germany) using a pelvic phased array coil. Patients were given 1 mg of glucagon into the muscle just before the test to reduce intestinal peristalsis. Table 2 summarizes the MR sequence parameters. First, conventional T1-weighted turbo spin-echo imaging with both axial and sagittal T2-weighted turbo spin-echo images and fat suppression and fat suppression exclusion was performed. Next, DW sequences were obtained from the axial plane using a single-shot echo plane image using the sensitivity coding technique. The b values corresponding to the diffusion detection gradient were 0 and 1,000 mm²/sec. T1- and T2-weighted and DW images were acquired with a cut thickness of 5 mm and a cutoff interval of 1 mm. The motion search gradient pulses were arranged in 3 orthogonal directions. Finally, PW...
sequences were performed on all tumors, with emphasis on the area of the solid component in the non-enhanced MRI. The images were acquired on an axial plane including the myometrium adjacent to the tumor on the optimal plane. Three-dimensional (3D), radiofrequency, and time resolved angiography stochastic trajectories (TWISTs) images (GRAPPA factor 2; Simens Healthcare, Erlangen, Germany) were used. Conventional dynamic contrast enhancement images were obtained using the TWIST technique. Gadolinium chelate (Gadovist; Bayer, Germany) was intravenously injected at a concentration of 0.1 mmol per/kg. Injection was performed with a high-pressure automatic injector (Medrad Spectris, Polkchach, Germany). The flow rate of 2 mL/sec was equivalent to 5 seconds of transient injection up to 120 mL. Then, 20 mL isotonic saline was immediately injected at the same flow rate.

Two experienced radiologists (10 and 12 years of abdominal imaging) analyzed the masses according to the following criteria: size, bilaterality, presence of multiple locules with various signal intensities, multiseptation, presence of solid component, presence of multiple, peritoneal seeding, and lymphadenopathy. Solid portions in cystic tumors refers to the proliferation, solid portion, and thickened septum of the wall or septum of the mass, as defined by Timmerman et al. [14]. All of the solid components showed enhancement after contrast injection. On T2-weighted image (T2WI), the signal intensity in the solid component was low or intermediate compared with myometrium. Two radiologists referenced the region of interest (ROI) (average, 10.2 mm; range, 8.8–12.8 mm in the largest dimension) with reference to a T2WI. The ROI was selected for each of the 3 regions with relatively low signal intensities in the solid phase, and then the mean value was calculated as the representative value for the calculated values of the diffusivity in each ROI. In order not to include the edge of the solid portion, the ROI is mainly included in the center portion. Similar to the method of calculating the current apparent diffusion coefficient (ADC), a ROI average of 10.0 mm (range, 8.0–12.0 mm in the largest dimension) was set for the same region to derive the time course enhancement pattern of the solid component. Perfusion coefficients were determined using commercial perfusion analysis software (Syngo Tissue 4D; Siemens Medical Solutions, Erlangen, Germany). In addition, color maps were fused to T2WIs.

To calculate the contrast ratio ($K_{\text{trans}}$) and the extracellular and extracellular fraction ($V_e$) between the vessels and the tissues, a known Tofts model was applied. When using the Tofts model, we used the estimated mean values from various clinical perfusion imaging studies to evaluate the contrast injection function that is always applied together.

To determine whether the distribution of BOT and stage I carcinomas differs statistically from their distribution on conventional MRI, we used Mann-Whitney and Fisher’s exact tests for each criterion for continuous and categorical criteria, respectively. The mean, standard deviation, and 95% confidence interval range of each DW and PW sequence parameter were then calculated. The quadratic $k$ coefficients were calculated to evaluate the agreement between the 2 radiologist observers ($k$-value, 0–0.19; poor, 0.20–0.39; fair, 0.40–0.59; moderate, 0.60–0.79; substantial, 0.80–1.00; excellent). A linear mixture model with both $p$-values was used to verify whether the differences between the distributions of each parameter were statistically significant. We also performed a receiver operating characteristic (ROC) curve analysis to evaluate the efficacy of conventional MRI, DW, and PW sequences in discriminating BOTs and stage

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T2-weighted turbo spin-echo</th>
<th>Axial T1-weighted turbo spin-echo</th>
<th>Axial DW echo-plana</th>
<th>Axial PW time resolved angiography stochastic trajectories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition time (msec)</td>
<td>3,100.0</td>
<td>3,700.0</td>
<td>500.0</td>
<td>5,500.0</td>
</tr>
<tr>
<td>Echo time (msec)</td>
<td>100.0</td>
<td>110.0</td>
<td>9.4</td>
<td>87.0</td>
</tr>
<tr>
<td>Echo train length</td>
<td>23</td>
<td>25</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Flip angle (degree)</td>
<td>150.0</td>
<td>150.0</td>
<td>149.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Sectional thickness (mm)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Intersection gap (mm)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Field of view (mm)</td>
<td>260 × 260</td>
<td>250 × 250</td>
<td>260 × 260</td>
<td>260 × 220</td>
</tr>
<tr>
<td>Matrix</td>
<td>380 × 260</td>
<td>380 × 260</td>
<td>320 × 250</td>
<td>160 × 80</td>
</tr>
<tr>
<td>Number of acquired signals</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Number of sections</td>
<td>25</td>
<td>30</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Acquisition time (sec)</td>
<td>150</td>
<td>165</td>
<td>25</td>
<td>110</td>
</tr>
</tbody>
</table>

DW, diffusion-weighted; PW, perfusion-weighted.

Table 2. Magnetic resonance imaging protocols

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I carcinoma. The area under the ROC curve (AUC) was used to determine diagnostic performance and the sensitivity and specificity were calculated from this curve analysis. Multivariate logistic regression analysis was performed to determine whether the combination of conventional MRI findings and the associated parameters such as ADC, $K^{trans}$, and $V_e$ improved the differentiation between BOTs and stage I carcinomas. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

**Results**

Table 3 summarizes the features of conventional MR sequence for BOTs and stage I carcinomas. The most prevalent features of stage I carcinoma were bilaterality (17 of 53 patients, 53%), peritoneal implants (9 of 14, 64%), and lymphadenopathy (4 of 8 patients, 50%). There was no statistically significant difference in size, multilocularity, the presence of loculi with various signal intensities, the presence of multiple septa, and distributions of solid components. Table 4 summarizes the 2 radiologists’ measurement results of the prevalence of the ADC, $K^{trans}$, and $V_e$ values for BOTs and stage I carcinomas. A case of BOTs and stage I carcinoma is presented (Figs. 1, 2).

There was good consensus between the radiologists for the values (BOT, $k = 0.850$; stage I carcinoma, $k = 0.890$). The linear composite model of dispersion showed that the distribution of the ADC was significantly different between BOTs and stage I carcinomas ($p < 0.03$). In this analysis, multiple lesions of a giv-

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**Table 3. Conventional MR sequence characteristics of borderline tumors and stage I carcinomas**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of findings</th>
<th>Borderline tumors (n = 38)</th>
<th>Stage I carcinomas (n = 32)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean patient age (yr)</td>
<td>70</td>
<td>40.8 ± 14.2</td>
<td>43.2 ± 13.2</td>
<td>0.58$^{a}$</td>
</tr>
<tr>
<td>Mean lesion size (cm)</td>
<td>70</td>
<td>12.5 ± 4.4</td>
<td>14.1 ± 5.2</td>
<td>0.42$^{a}$</td>
</tr>
<tr>
<td>Bilaterality</td>
<td>70</td>
<td>16 (6/38)</td>
<td>53 (17/32)</td>
<td>0.009$^{b}$</td>
</tr>
<tr>
<td>Multilocularity</td>
<td>48</td>
<td>59 (13/22)</td>
<td>69 (18/26)</td>
<td>0.01$^{b}$</td>
</tr>
<tr>
<td>Loculi with different signal intensity</td>
<td>25</td>
<td>50 (5/10)</td>
<td>47 (7/15)</td>
<td>0.38$^{b}$</td>
</tr>
<tr>
<td>Multiseptation</td>
<td>50</td>
<td>71 (20/28)</td>
<td>64 (14/22)</td>
<td>0.08$^{b}$</td>
</tr>
<tr>
<td>Solid components</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Vegetation</td>
<td>32</td>
<td>58 (7/12)</td>
<td>65 (13/20)</td>
<td>0.08$^{a}$</td>
</tr>
<tr>
<td>Solid portion</td>
<td>20</td>
<td>57 (4/7)</td>
<td>62 (8/13)</td>
<td>0.10$^{a}$</td>
</tr>
<tr>
<td>Thickened septa</td>
<td>18</td>
<td>62 (5/8)</td>
<td>70 (7/10)</td>
<td>0.08$^{a}$</td>
</tr>
<tr>
<td>Ascites</td>
<td>31</td>
<td>40 (4/10)</td>
<td>43 (9/21)</td>
<td>0.03$^{a}$</td>
</tr>
<tr>
<td>Peritoneal implants</td>
<td>20</td>
<td>33 (2/6)</td>
<td>64 (9/14)</td>
<td>0.03$^{a}$</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>8</td>
<td>0</td>
<td>50 (4/8)</td>
<td>0.001$^{b}$</td>
</tr>
<tr>
<td>Signal intensity of solid component on T2</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Low signal intensity</td>
<td>25</td>
<td>43 (6/14)</td>
<td>45 (5/11)</td>
<td>0.10$^{b}$</td>
</tr>
<tr>
<td>Intermediate signal intensity</td>
<td>45</td>
<td>54 (15/28)</td>
<td>64 (11/17)</td>
<td>0.09$^{b}$</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number. Numbers in parentheses are numbers of lesions.

$^{a}$Calculated with the Mann-Whitney test. $^{b}$Calculated with the Fisher exact test.

**Table 4. Results of the comparison of ADC, $K^{trans}$, and $V_e$ values for borderline tumors and stage I carcinomas between 2 radiologists**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Radiologist 1</th>
<th></th>
<th>Radiologist 2</th>
<th></th>
<th>$k$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>95% CI</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Borderline tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC ($× 10^{-3}$ mm$^2$/sec)</td>
<td>1.151</td>
<td>0.282</td>
<td>1.201-1.335</td>
<td>1.132</td>
<td>0.301</td>
</tr>
<tr>
<td>$K^{trans}$ (/min)</td>
<td>0.236</td>
<td>0.054</td>
<td>0.201-0.284</td>
<td>0.258</td>
<td>0.051</td>
</tr>
<tr>
<td>$V_e$</td>
<td>0.148</td>
<td>0.053</td>
<td>0.132-0.197</td>
<td>0.156</td>
<td>0.056</td>
</tr>
<tr>
<td>Stage I carcinomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC ($× 10^{-3}$ mm$^2$/sec)</td>
<td>1.053</td>
<td>0.214</td>
<td>0.924-1.103</td>
<td>1.087</td>
<td>0.195</td>
</tr>
<tr>
<td>$K^{trans}$ (/min)</td>
<td>0.309</td>
<td>0.053</td>
<td>0.291-0.359</td>
<td>0.326</td>
<td>0.038</td>
</tr>
<tr>
<td>$V_e$</td>
<td>0.305</td>
<td>0.041</td>
<td>0.288-0.374</td>
<td>0.318</td>
<td>0.046</td>
</tr>
</tbody>
</table>

SD, standard deviation; CI, confidence interval; ADC, apparent diffusion coefficient.
en patient were randomly selected to ensure that one lesion of a certain type was correctly included in the analysis. Therefore, it is necessary to correct the analysis by the fixation effect, and the distribution of ADC is significantly different between the BOT and the stage I carcinoma ($p=0.02$). Fig. 3 shows the distribution of individual ADCs. Although the mean ADCs differ significantly, the distribution of some values overlap. The mixed model analysis of variance showed that $K_{trans}$ and $V_e$ values were significantly different between BOTs and stage I carcinomas ($p<0.01$). In this analysis, multiple lesions in a given patient were randomly selected. Estimates of the fixation effect indicate that the distribution of $K_{trans}$ and $V_e$ values is significantly different between BOTs and stage I carcinomas ($p=0.009$ and $p=0.02$, respectively). The ROC of the ADC yielded AUCs of 0.58 and 0.68 for differentiation between BOTs and stage I carcinomas. The ROC of the ADC yielded AUCs of 0.58 and 0.68.

Fig. 1. Images of a serous cystadenoma borderline tumor in a 46-year-old woman. (A) T2-weighted fast spin-echo axial MR image shows a right ovarian tumor with cystic and solid components as solid portions (arrows) with low signal intensity. Ascites (arrowhead) is shown. (B) ADC map obtained at $b=1,000 \text{ mm}^2/\text{sec}$ shows restricted diffusion in the solid portions (arrows, measured mean ADC map=$1.12\times10^{-3} \text{ mm}^2/\text{sec}$). (C) $K_{trans}$ and $V_e$ map color overlain on a T2-weighted MR image shows increased $K_{trans}$ and $V_e$ values throughout the solid portions (measured $K_{trans}$ and $V_e$ of the ROI$_2=0.254/\text{min}$ and $0.150$). (D) Relative enhancement time fitting curve of the solid component of the borderline tumor is shown. MR, magnetic resonance; ADC, apparent diffusion coefficient; ROI, region of interest.
for differentiation between BOTs and stage I carcinomas. The AUCs of $K^{\text{trans}}$ were 0.78 and 0.82, and those of $V_e$ were 0.70 and 0.72 (Fig. 4). DW sequences of BOTs and stage I carcinomas showed relatively low diagnostic performance, while PW sequences showed slightly higher diagnostic performance. Fig. 5 shows the AUC of the ADC, $K^{\text{trans}}$, and $V_e$ parameters.

**Discussion**

The results of this study demonstrate the diagnostic value of DW and PW sequence techniques in discriminating between BOTs and stage I carcinomas. In this study, all of the solid components on T2WIs showed low or intermediate signal intensity and could not be used as a reference for discrimination. Previous studies have suggested that bilaterality, peritoneal implants, and lymph-
adenopathy may be useful in the diagnosis of stage I carcinoma. It is known that BOTs have a smaller solid area, thinner septa, and lower cancer antigen-125 values when they are in the solid and septum [9]. Epithelial tumors appear to be predominantly cystic, regardless of the margin tumors and carcinomas, and contain varying degrees of solid components. As in many previous studies of conventional MRI for the differential diagnosis of BOTs and stage I carcinomas, sensitivity and specificity were also low in this study [6,12].

Recent studies of the DW sequences related to solid components in ovarian tumors have been reported but are limited in number [5,15]; the mean ADC value of the ovarian carcinoma was $1.03 \times 10^{-3}$ mm$^2$/sec and the sensitivity and specificity were 74% and 80% for the differentiation between BOTs and stage I carcinomas, using a cutoff value of $1.15 \times 10^{-3}$ mm$^2$/sec. In the present study, the mean ADCs of BOTs and stage I carcinomas were $1.12 \times 10^{-3}$ mm$^2$/sec and $1.05 \times 10^{-3}$ mm$^2$/sec, respectively. Despite various reports that a low ADC value is more prevalent in carcinoma, wide ranges of values have been seen. Although these values do not recognize pathologic variation in cell density in BOTs and stage I carcinomas, the use of a single ADC to represent all solid components is considered a cause of this result. Nevertheless, the results of this study show significant differences in mean ADC between BOTs and stage I carcinomas. Some carcinomas may have a small necrotic or cystic area in the solid component and may appear as solid tissue with accumulation of cystic fluid intercalated between the ovarian processes. These have contributed to increasing diffusion. However, in general, carcinoma has more cellularity and a denser substrate. These differences can be explained by a further reduction of the ADC in carcinoma. Therefore, DW sequences may be helpful to differentiate between BOTs and stage I carcinomas, although the ADCs partially overlap.

The role of PW sequences in the diagnosis of ovarian tumors is debatable. Previous studies have described the initial area under

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**Fig. 3.** Box and whisker plot of ADC values for borderline tumors and stage I carcinomas. Data box=individual ADC value, horizontal lines=average and associated 95% confidence intervals. ADC, apparent diffusion coefficient.

**Fig. 4.** ROC curves of ADC, $V_v$, and $K^{trans}$ parameters in the differentiation of borderline tumors (A) and stage I carcinomas (B). 1=ADC, 2=$V_v$, and 3=$K^{trans}$. ROC, receiver operating characteristic; ADC, apparent diffusion coefficient.

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In this study, contrast enhancement characteristics were different between BOTs and stage I carcinomas, and quantitative perfusion imaging parameters such as $K^\text{trans}$ and $V_e$ were helpful in differentiating between BOTs and stage I carcinomas. In brain, prostate, and breast tumors, diagnostic information from multiple parameters, including DW and PW sequences, is obtained and provides better accuracy than is possible with the use of a single parameter [21-26].

In this study, the ADC has low statistical significance in the logistic regression model analysis and the AUC is only 0.71. Furthermore, ADC is less effective than $K^\text{trans}$ and $V_e$ in differentiating between BOTs and stage I carcinomas, but diagnostic accuracy when combined with $K^\text{trans}$ and $V_e$ increases sensitivity with a low false positive rate. Prospective study of the association of DW and PW sequences is needed to evaluate the clinical usefulness of this approach to discriminate between BOTs and stage I carcinomas.

This study has some limitations. First, histopathologically proven cases involving only solid components are considered. This might have introduced selection and verification bias. In addition, there were few cases of BOTs and it was difficult to perform precise analysis to distinguish them from stage I carcinomas. Second, the current implementation plan for MRI has limitations with respect to planar resolution and image sharpness. These can affect the computation of quantitative parameters of the DW and PW sequences. In cases where the amount of solid content is small, the accuracy of DW and PW sequences may decrease due to the increase in motion artifacts. However, recent techniques such as multi-shot DW and volume isotropic turbo spin-echo acquisition segmented 3D sequences have enabled improved quantification of tissue components and dynamic signal time course features. Third, only 57 patients underwent imaging with both DW and PW sequences. Larger populations are needed to verify whether there is a meaningful difference between conventional MRI with both DW and PW sequences compared with the respective ones. In addition, in this study, the diagnosis could not be corrected for the same tumor misdiagnosed on DW and PW sequences. In some cases, the PW sequence was useful for diagnosis and the DW sequence was irrelevant, and in other cases, the opposite occurred. Finally, these techniques require external validation, such as establishing a firm cutoff value for the standardized ADC, $K^\text{trans}$, and $V_e$ for universal use. Because the accuracy of this study was based on thresholds set from the same population, performance may have been overestimated. Improvement of DW and PW techniques enables evaluation of the overall solid content, thereby reducing the possibility of overlapping parameters. Therefore, the sensitivity and specificity for predicting the solidity of a solid component can be improved.

In conclusion, the parameters of DW and PW sequences were
significantly different between BOTs and stage I carcinomas. Although the use of a quantitative DW sequence alone is not effective for discrimination, combination of the ADC, K^trans, and V_1 can improve the differentiation compared to the use of the ADC alone.

**Conflicts of interest**

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

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**References**


Determining the correlation between outdoor heatstroke incidence and climate elements in Daegu metropolitan city

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Background: Heatstroke is one of the most serious heat-related illnesses. However, establishing public policies to prevent heatstroke remains a challenge. This study aimed to investigate the most relevant climate elements and their warning criteria to prevent outdoor heatstroke (OHS).

Methods: We investigated heatstroke patients from five major hospitals in Daegu metropolitan city, Korea, from June 1 to August 31, 2011 to 2016. We also collected the corresponding regional climate data from Korea Meteorological Administration. We analyzed the relationship between the climate elements and OHS occurrence by logistic regression.

Results: Of 70 patients who had heatstroke, 45 (64.3%) experienced it while outdoors. Considering all climate elements, only mean heat index (MHI) was related with OHS occurrence (p=0.019). Therefore, the higher the MHI, the higher the risk for OHS (adjusted odds ratio, 1.824; 95% confidence interval, 1.102–3.017). The most suitable cutoff point for MHI by Youden’s index was 30.0°C (sensitivity, 77.4%; specificity, 73.7%).

Conclusion: Among the climate elements, MHI was significantly associated with OHS occurrence. The optimal MHI cutoff point for OHS prevention was 30.0°C.

Keywords: Climate; Heatstroke; Incidence; Meteorology; Policy

Introduction

Increasing greenhouse gas emissions and consequent global warming continue to be major environmental issues. The average global temperature in July 2016 was 0.82°C higher than the mean temperatures from 1951 to 1980 [1]. Global warming may cause previously unobserved weather patterns, including extreme heat and cold. Prolonged exposure to high temperatures can cause various heat-related illnesses, such as edema, cramps, syncope, exhaustion, and heatstroke, which can lead to death in severe cases [1-6]. For example, heatwaves, excessively hot weather lasting for days or weeks, claimed 14,800 lives in France in 2003 and 55,000 lives in Russia in 2010. In 2009, Australia reported a 14-fold increase in hospitalizations due to heat-related illnesses...
In Korea, heatwaves caused 442 heat-related deaths from 1991 to 2011; in Seoul, over 80 excess deaths occurred during the day in 1994 [7,8].

One of the most serious heat-related illnesses is heatstroke. It is typically characterized by a core body temperature exceeding 40°C and central nervous system (CNS) abnormalities, such as altered mental status or seizure [2-6,9]. Older people, people with dehydration, individuals diagnosed with alcoholism, and individuals with previous neuropsychiatric disorders are more susceptible to heatstroke [6,9,10]. A heatwave that affected Pakistan during Ramadan in 2015 caused heatstroke in 78 patients within a period of 3 days; unfortunately, 42 of these patients died [11]. Several countries have implemented heat-health alert systems to prevent the occurrence of such heat-related health conditions. However, the specific methods and warning criteria for these systems vary by country [12-16]. The Korea Meteorological Administration (KMA) is currently operating a heat alert system based on maximum daily temperatures [17-19]. Based on this alert system, the number of summer heatwaves (maximal daily temperature over 33°C) in Daegu, one of the hottest regions in Korea, have increased from 25 days in 2011 to 32 days in 2016 and 51 days in 2013 [17]. However, this system does not consider the heat index, which is a measure of the actual heat-related stress in the human body.

Although there have been numerous studies regarding heatstroke, most of them have focused on its pathophysiology or complications. Only a few studies have examined the correlations between heatstroke and various climate elements. Previous studies aimed at identifying the most predictive climate elements and warning criteria for preventing heatstroke are limited. Therefore, we aimed to examine the correlations between outdoor heatstroke (OHS) incidence and climate elements in a single metropolitan city in Korea in order to determine the most relevant climate elements and their warning criteria to prevent heatstroke.

**Materials and methods**

1. **Study participants**

To compare the differences in the climate elements between the days when the heatstroke occurred and days that heatstroke did not occur, we considered all days during the summer (June 1 to August 31) of 2011 to 2016. To identify all heatstroke cases in the Daegu metropolitan city in those periods, we reviewed the medical records of 237,835 patients who were admitted to the emergency room (ER) during those periods in one regional emergency medical center and four local emergency medical centers.

The diagnosis of heatstroke was based on a patient’s medical history and clinical features after ruling out other febrile diseases. In order to determine the appropriate study participants, the following inclusion criteria were used. An age limit of ≥ 8 years was applied to ensure diagnostic accuracy, as the clinical presentation of heatstroke is similar to that of septicemia in children aged < 8 years [3]. With regard to the inclusion criteria, using the final diagnosis is simple but it is likely that the diagnostic input may be missing; hence, we used the following two criteria: (1) having an initial body temperature of ≥ 39°C upon admission and (2) classified using diagnosis codes that indicate heat-related illnesses. A body temperature limit of ≥ 39°C upon admission was used to minimize missing cases, as the body temperature of patients could have been measured as < 40°C when they arrived at the ER [10,20,21]. A total of 4,723 patients aged ≥ 8 years who met one of these criteria were initially selected. Subsequently, individuals (1) with obviously febrile disease, (2) without history of heat exposure, and (3) with no CNS abnormalities were excluded; after excluding these patients, 70 were ultimately classified as heatstroke patients [2,5,6] (Fig. 1). To analyze the relationship between heatstroke incidence and climate elements, we only included OHS patients (excluding indoor heatstroke [IHS] patients).

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**Fig. 1.** Flow chart of study population. CNS, central nervous system.
and those who developed heatstroke in unknown locations.

2. Data collection
We retrospectively reviewed the medical records of patients admitted to each emergency medical center. With regard to the general characteristics, age, sex, location, circumstances when heatstroke occurred, and arrival type and time were considered. With regard to the clinical characteristics, onset time, body temperature upon arrival, state of consciousness upon arrival, systolic blood pressure upon arrival, underlying diseases, intubation, and treatment outcome were considered. If the onset time was unknown, the time when the individual was last observed as normal was determined. With regard to the outcome, individuals whose records confirmed a discharge following clinical recovery (i.e., normal consciousness level and body temperature) were classified as having good outcomes. Patients whose records indicated fatality or who were transferred to another medical center, as they had no signs of clinical recovery, were classified as having poor outcomes.

The following climate elements for the corresponding time period were obtained from the KMA website: the minimum temperature, maximum temperature, mean temperature, mean relative humidity, mean wind speed, mean daylight hours, heatwave, and daily mean heat index (MHI) in the Daegu area. The daily MHIs obtained were classified as follows: very low (<27°C), low (27–31°C), ordinary (32–40°C), high (41–53°C), very high (54–65°C), and dangerous (≥66°C) according to the standards currently used by the KMA. Data collection of this retrospective study was commenced after approval by the Yeungnam University Hospital Institutional Review Board (IRB No. 2017-03-023).

3. Statistical analysis
The distributions of MHIs and OHS incidence by stage are presented (Fig. 2). To identify the individual effects of daily climate elements on OHS occurrence, a logistic regression analysis was performed with each climate element as an independent variable and OHS occurrence as the dependent variable. Simultaneously, to identify the element that was closely correlated with OHS occurrence, a logistic regression analysis was performed using all elements as independent variables, except the days when IHS occurred. To determine the appropriate cutoff point for the most correlated climate element to prevent OHS, the sensitivity, specificity, and Youden’s index (sensitivity+specificity–1) were calculated.

All statistical analyses were performed using IBM SPSS version 21.0 (IBM Co., Armonk, NY, USA), with the significance level set at \( p < 0.05 \).

Results
Of the total 70 heatstroke patients, 45 were OHS patients, 17 were IHS patients, and 8 had heatstroke in an unknown location. The baseline characteristics of heatstroke patients are described in Table 1.

There were no significant differences in the climate elements between IHS and OHS patients. Furthermore, MHI levels between the two groups were also found to be insignificant. All pa-
Patients developed heatstroke at an MHI level below “ordinary” (Table 2).

During the study period (552 days), the day of heatstroke occurred was 47 days, including the 34 days in which OHS occurred. The MHI of the 34 days in which OHS occurred were higher than that of the other 518 days (32.1 ± 4.5°C and 26.1 ± 4.2°C, respectively). A 1°C increase in the MHI was significantly associated with a 1.393-fold increase in the risk for OHS (95% confidence interval [CI], 1.255–1.546). The mean, maximum, and minimum daily temperatures and diurnal temperature range of OHS occurred days were also greater than those of the other days. A 1°C increase in the mean, maximum, and minimum daily temperatures and diurnal temperature range was significantly associated with a 1.710-fold (95% CI, 1.436–2.036), 1.787-fold (95% CI, 1.489–2.145), 1.450-fold (95% CI, 1.246–1.688), and 1.352-fold (95% CI, 1.175–1.557) increase in the risk for OHS, respectively. Similarly, a 1-hr increase in daylight hours was significantly associated with a 1.397-fold increase

Table 1. Baseline characteristics of heatstroke patients according to the place

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 70)</th>
<th>Outdoor (n = 45)</th>
<th>Indoor (n = 17)</th>
<th>Unknown (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.2 ± 21.0</td>
<td>62.1 ± 22.8</td>
<td>71.7 ± 16.6</td>
<td>60.4 ± 16.8</td>
</tr>
<tr>
<td>Male</td>
<td>50</td>
<td>36 (80.0)</td>
<td>7 (41.2)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>Type of arrival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public EMS</td>
<td>44</td>
<td>24 (53.3)</td>
<td>17 (100.0)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>From other hospital</td>
<td>24</td>
<td>19 (42.2)</td>
<td>0 (0.0)</td>
<td>5 (62.5)</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>2 (4.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>BT when arrival at hospital (°C)</td>
<td>39.5 ± 1.7</td>
<td>39.0 ± 1.7</td>
<td>41.0 ± 0.7</td>
<td>39.6 ± 1.8</td>
</tr>
<tr>
<td>SBP when arrival at hospital (mmHg)</td>
<td>118.0 ± 31.0</td>
<td>115.6 ± 29.9</td>
<td>130.6 ± 33.9</td>
<td>103.8 ± 24.4</td>
</tr>
<tr>
<td>Mental status when arrival at hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alert</td>
<td>21</td>
<td>14 (31.1)</td>
<td>5 (29.4)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Drowsy</td>
<td>25</td>
<td>16 (35.6)</td>
<td>4 (23.5)</td>
<td>5 (62.5)</td>
</tr>
<tr>
<td>Stupor</td>
<td>7</td>
<td>5 (11.1)</td>
<td>1 (5.9)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Coma</td>
<td>17</td>
<td>10 (22.2)</td>
<td>7 (41.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>13 (28.9)</td>
<td>12 (70.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Diabetics mellitus</td>
<td>11</td>
<td>7 (15.6)</td>
<td>4 (23.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8</td>
<td>4 (8.9)</td>
<td>3 (17.6)</td>
<td>1 (12.5)</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).
EMS, emergency medical service; BT, body temperature; SBP, systolic blood pressure.

Table 2. Climate elements and location of heatstroke

| Variable                  | Outdoor (n = 45) | Indoor (n = 17) | Unidentified (n = 8) | Total (n = 70) | p-value*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Climate element</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean heat index (°C)</td>
<td>32.6 ± 4.6</td>
<td>33.7 ± 2.4</td>
<td>34.5 ± 1.4</td>
<td>33.1 ± 4.0</td>
<td>0.228</td>
</tr>
<tr>
<td>Mean air temperature (°C)</td>
<td>29.4 ± 2.9</td>
<td>30.4 ± 1.8</td>
<td>30.8 ± 0.9</td>
<td>29.8 ± 2.5</td>
<td>0.106</td>
</tr>
<tr>
<td>Maximal air temperature (°C)</td>
<td>35.2 ± 2.5</td>
<td>36.0 ± 1.8</td>
<td>36.2 ± 0.9</td>
<td>35.5 ± 2.2</td>
<td>0.252</td>
</tr>
<tr>
<td>Minimum air temperature (°C)</td>
<td>24.3 ± 3.3</td>
<td>25.5 ± 2.1</td>
<td>25.8 ± 1.4</td>
<td>24.7 ± 3.0</td>
<td>0.100</td>
</tr>
<tr>
<td>Daily temperature range (°C)</td>
<td>11.0 ± 1.9</td>
<td>10.5 ± 1.5</td>
<td>10.3 ± 1.9</td>
<td>10.8 ± 1.8</td>
<td>0.394</td>
</tr>
<tr>
<td>Mean relatively humidity (%)</td>
<td>62.7 ± 8.6</td>
<td>60.2 ± 6.9</td>
<td>61.5 ± 6.8</td>
<td>61.9 ± 8.0</td>
<td>0.301</td>
</tr>
<tr>
<td>Mean wind speed (m/sec)</td>
<td>1.7 ± 0.4</td>
<td>1.9 ± 0.5</td>
<td>1.8 ± 0.4</td>
<td>1.8 ± 0.4</td>
<td>0.155</td>
</tr>
<tr>
<td>Amount of sunshine (hr)</td>
<td>9.7 ± 2.4</td>
<td>10.0 ± 3.5</td>
<td>9.5 ± 2.6</td>
<td>9.8 ± 2.7</td>
<td>0.722</td>
</tr>
<tr>
<td>Heat index stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>7 (15.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>7 (10.0)</td>
<td>0.302</td>
</tr>
<tr>
<td>Low</td>
<td>9 (20.0)</td>
<td>4 (23.5)</td>
<td>0 (0.0)</td>
<td>13 (18.6)</td>
<td></td>
</tr>
<tr>
<td>Ordinary</td>
<td>29 (64.4)</td>
<td>13 (76.5)</td>
<td>8 (100.0)</td>
<td>50 (71.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation or number (%).
*Analysis between outdoor and indoor cases by t-test and Fisher’s exact test.
risk for OHS (95% CI, 1.227–1.589).

A 1% increase in mean humidity was significantly associated with a 0.938-fold reduction in the risk for OHS (95% CI, 0.909–0.969). A 1 m/sec increase in the mean wind speed was also significantly associated with a 0.371-fold reduction in the risk of OHS (95% CI, 0.199–0.694). However, when all climate elements were considered simultaneously, only the daily MHI was found to significantly increase OHS risk: a 1°C increase in the daily MHI resulted in a 1.824-fold (95% CI, 1.102–3.017) increase in OHS risk (Table 3).

The sensitivity, specificity, and Youden’s index, with exception of the days when heatstroke occurred indoors, were calculated to determine the warning criteria for OHS. The most suitable cutoff point was confirmed to be a daily MHI of 30.0°C (Youden’s index, 0.511; sensitivity, 77.4%; specificity, 73.7%; Table 4).

Discussion

Extreme weather phenomena due to global warming continue to occur worldwide, with a significant impact on human life [22-26]. Heatwaves are one of the most concerning meteorological conditions expected to cause damage as climate change progresses [7, 27-29]. An individual affected by heatstroke loses the ability to regulate body temperature due to damage to the hypothalamic thermoregulatory system following prolonged exposure to high temperatures [30, 31]. A sustained elevated core temperature can damage a number of internal organs, which can lead to a life-threatening situation [2-4, 21]. Thus, many countries have been making efforts to reduce the disease burden associated with heat-related illnesses, including the implementation of effective heat alert systems [15, 16, 32-37]. An effective alert system requires the selection of the most appropriate climate elements and their warning criteria to predict heatstroke occurrence [38].

In the literature, there are conflicting findings regarding which elements are most predictive of heatstroke occurrence. Some studies have reported that heat index is strongly correlated with the number of patients admitted to the ER due to heat-related illnesses, which suggests the application of the heat index as a predictor of heat-related illness [19, 39, 40]. Other studies have reported that the daily maximum temperature is a more appropriate predictor of heatstroke occurrence than the heat index [8, 28, 41]. Heat index is the biometeorological indicator used by the United States National Weather Service [19]. It is calculated by measuring the dry-bulb Fahrenheit temperature and relative humidity to estimate the heat burden according to outdoor conditions.

Based on our study, various climate elements, including the mean, maximum, and minimum daily temperatures; diurnal temperature variations; daylight hours; and the MHI, were significant risk factors for OHS occurrence, whereas mean humidity and mean wind speed were significant protective factors. This finding is congruent to the fact that, aside from prolonged exposure to high heat, dry conditions and poor ventilation increase the risk of heatstroke. However, after simultaneously considering these climate elements, we found that the MHI was the only effective predictor of OHS incidence. The risk of OHS increased significantly by 1.82-fold for each 1°C increase in the MHI. The finding that the MHI was the only significant predictor of OHS may be attributed to the fact that the MHI is a biometeorological index that incorporates both dry bulb temperature and relative humidity for measuring climate-related heat stress in the human body. Thus, the heat index, which reflects both air temperature and humidity, may be more useful for predicting OHS incidence than the maximum daily temperature, which only reflects air temperature.

In South Korea, the KMA has been operating heatwave alerts

### Table 3. Association between climate elements and days of outdoor heatstroke by logistic regression analysis

<table>
<thead>
<tr>
<th>Outdoor heatstroke day</th>
<th>Yes (n = 34 days)</th>
<th>Noa (n = 508 days)</th>
<th>OR [95% CI]</th>
<th>eORb [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean air temperature (°C)</td>
<td>28.9 ± 2.7 [22-32]</td>
<td>25.0 ± 2.9 [17-32]</td>
<td>1.654 [1.375-1.988]</td>
<td>0.776 [0.315-1.913]</td>
</tr>
<tr>
<td>Maximal air temperature (°C)</td>
<td>34.8 ± 2.4 [28-38]</td>
<td>29.9 ± 3.6 [19-37]</td>
<td>1.713 [1.418-2.069]</td>
<td>0.671 [0.265-1.669]</td>
</tr>
<tr>
<td>Daily temperature range (°C)</td>
<td>10.4 ± 1.9 [7-15]</td>
<td>8.2 ± 2.8 [1-16]</td>
<td>1.356 [1.166-1.578]</td>
<td>1.770 [0.732-4.282]</td>
</tr>
<tr>
<td>Mean relatively humidity (%)</td>
<td>60.7 ± 8.8 [36-76]</td>
<td>69.1 ± 11.6 [32-97]</td>
<td>0.941 [0.909-0.973]</td>
<td>0.950 [0.879-1.027]</td>
</tr>
<tr>
<td>Mean wind speed (m/sec)</td>
<td>1.2 ± 0.5 [1-3]</td>
<td>1.7 ± 0.8 [0-5]</td>
<td>0.392 [0.201-0.764]</td>
<td>0.440 [0.180-1.078]</td>
</tr>
<tr>
<td>Amount of sunshine (hr)</td>
<td>9.4 ± 2.5 [2-12]</td>
<td>5.1 ± 4.0 [0-13]</td>
<td>1.396 [1.212-1.608]</td>
<td>1.220 [0.958-1.553]</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation [minimum, maximum].

OR, odds ratio; CI, confidence interval; aOR, adjusted OR.

a) Excepted 10 days of indoor heatstroke only.
b) Calculated considering all climates elements together.
system based on the maximum daily temperature. Additionally, the KMA also provides daily heat index values, using the heat index categories of low (27–31°C), ordinary (32–40°C), high (41–53°C), very high (54–65°C), and dangerous (≥ 66°C) based on the heat index classifications from the National Oceanic and Atmospheric Administration [17]. However, these categories are not actively used as an alert index as there is no scientific evidence indicating the most appropriate cutoff point to predict heatstroke occurrence [42].

During the study period (552 days), 332 days were categorized as very low risk, 129 days as low risk, and 91 days as ordinary risk, based on the heat index category. Significantly, none of the days were categorized as high, very high, or dangerous. Of the 34 days in which heatstroke occurred, 22 days were categorized as ordinary risk, 12 days as low risk, and 5 days as very low risk (Fig. 2). The most appropriate cutoff value to predict OHS occurrence was 30.0°C. Considering these facts, the current KMA heat index classification system has low utility as a heatstroke alert system. Unfortunately, the system is potentially dangerous because it invariably provides the public with a false sense of heat safety.

Thus, all countries, including Korea, should implement an effective heat-safety alert system that reflects the characteristics of their specific location.

There were several limitations to our study. First, we did not distinguish the difference between classic and exertional heatstroke; therefore, weather conditions might differently influence the types of heatstroke. Second, we had difficulties identifying the precise location of a heatstroke occurrence based only on a medical record review. Third, although climate conditions may be different locally within the same region at the same time, we could not consider this variability using the secondary data obtained from the KMA website. Therefore, it was impossible to accurately identify the real-life climate elements that affected the areas of OHS occurrence. Finally, as we did not use an individual level analysis such as case-crossover design, we could not adjust various covariates including patient’s age, sex, underlying health status, and so on.

Nevertheless, to the best of our knowledge, this is the first Korean study to investigate the most relevant climate elements and their warning criteria to prevent heatstroke, with participation from all regional and local emergency medical centers. Furthermore, a large-scale medical review and regular quality control of the data were performed to ensure data accuracy and identify as many patients with suspected heatstroke as possible. Finally, we examined the correlations between heatstroke and climate elements using KMA’s climate data, identified the MHI as the most effective predictor of OHS incidence, and presented an appropriate cutoff value for the alert system.

In the short term, it will be difficult to improve the environmental risk factors (including climate elements) that contribute to heat-related illnesses. However, the development and implementation of an effective alert system to inform the public of health risks and adequate response measures can provide a substantial preventive effect. Further systematic studies would be beneficial for the development of an effective heat alert system.

We examined the correlations between climate elements and OHS in patients who were admitted to the local and regional emergency medical centers in Daegu. A total of 70 heatstroke patients were identified, 45 of whom experienced heatstroke outdoors. Although various climate elements were found to be correlated with heatstroke incidence, the MHI was closely associated with heatstroke incidence when all elements were considered simultaneously. The most predictive MHI cutoff point for OHS prevention was 30.0°C. Further studies are required to develop an effective heat alert system that incorporates the biometeorological characteristics of a specific location.

Table 4. Sensitivity and specificity of outdoor heatstroke occurrence

<table>
<thead>
<tr>
<th>Cutoff point for MHI (°C)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Youden’s index</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.0</td>
<td>100.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>18.0</td>
<td>100.0</td>
<td>0.0</td>
<td>0.00</td>
</tr>
<tr>
<td>19.0</td>
<td>100.0</td>
<td>1.0</td>
<td>0.010</td>
</tr>
<tr>
<td>20.0</td>
<td>100.0</td>
<td>2.4</td>
<td>0.024</td>
</tr>
<tr>
<td>21.0</td>
<td>100.0</td>
<td>4.8</td>
<td>0.048</td>
</tr>
<tr>
<td>22.0</td>
<td>100.0</td>
<td>12.1</td>
<td>0.121</td>
</tr>
<tr>
<td>23.0</td>
<td>96.8</td>
<td>22.2</td>
<td>0.190</td>
</tr>
<tr>
<td>24.0</td>
<td>93.5</td>
<td>32.9</td>
<td>0.264</td>
</tr>
<tr>
<td>25.0</td>
<td>83.9</td>
<td>45.3</td>
<td>0.292</td>
</tr>
<tr>
<td>26.0</td>
<td>83.9</td>
<td>57.8</td>
<td>0.417</td>
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<tr>
<td>27.0</td>
<td>83.9</td>
<td>64.8</td>
<td>0.486</td>
</tr>
<tr>
<td>28.0</td>
<td>80.6</td>
<td>66.1</td>
<td>0.468</td>
</tr>
<tr>
<td>29.0</td>
<td>80.6</td>
<td>69.5</td>
<td>0.502</td>
</tr>
<tr>
<td>30.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>77.4</td>
<td>73.7</td>
<td>0.511</td>
</tr>
<tr>
<td>31.0</td>
<td>61.3</td>
<td>79.6</td>
<td>0.409</td>
</tr>
<tr>
<td>32.0</td>
<td>61.3</td>
<td>88.1</td>
<td>0.494</td>
</tr>
<tr>
<td>33.0</td>
<td>58.1</td>
<td>92.7</td>
<td>0.507</td>
</tr>
<tr>
<td>34.0</td>
<td>41.9</td>
<td>97.2</td>
<td>0.392</td>
</tr>
<tr>
<td>35.0</td>
<td>35.5</td>
<td>98.6</td>
<td>0.341</td>
</tr>
<tr>
<td>36.0</td>
<td>19.4</td>
<td>99.4</td>
<td>0.188</td>
</tr>
<tr>
<td>37.0</td>
<td>12.9</td>
<td>99.8</td>
<td>0.127</td>
</tr>
<tr>
<td>38.0</td>
<td>3.2</td>
<td>99.8</td>
<td>0.030</td>
</tr>
<tr>
<td>39.0</td>
<td>3.2</td>
<td>99.8</td>
<td>0.030</td>
</tr>
</tbody>
</table>

MHI, mean heat index.
<sup>a</sup>Most suitable cut-off point of a daily MHI.
Conflicts of interest

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

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References


Apathy syndrome in a patient previously treated with selective serotonin reuptake inhibitors for depression

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Keywords: Apathy; Depression; Serotonin reuptake inhibitor

Introduction

Apathy is a behavioral syndrome characterized by a decrease in interest, motivation, or initiation of action. Apathy may present in a similar manner as depression. However, Marin [1] emphasized the importance of differentiating between apathy and other psychiatric conditions, including depression, dementia, delirium, abulia, akinesia, despair, and demoralization. He proposed the following definition of apathy: a syndrome in which there is a primary absence of motivation that is not attributable to cognitive impairment, emotional distress, or diminished level of consciousness [1]. Many patients with apathy syndrome reported that “this feeling was unlike the lack of motivation they had sometimes experienced during prior episodes of depression,” or that “their feelings of apathy bore no relationship to depression.”

One reason for the importance of differentiating apathy syndrome from depression is that apathy syndrome has been reported in a number of patients receiving selective serotonin reuptake inhibitor (SSRI) treatment over the last decade [2]. Apathy also serves as a behavioral marker for rapidly progressing dementia, with a greater decline in cognitive, functional, and emotional impairment [3]. The presence of apathy is linked to deficits in the performance of activities of daily living and a functional decline [4]. Thus, the prompt recognition and treatment of apathy are crucial [4].

Here, we report the case of a patient who experienced apathy syndrome that was difficult to differentiate from depression and dementia. Written informed consent for the publication of this case report, approved by the institutional review board (YUMC 2017-12-022), was obtained from the patient.

Case

A 67-year-old woman with a remote history of depression was referred to our clinic due to the presentation of resistant depressive symptoms despite being treated with multiple antidepressant drugs, including escitalopram, paroxetine, duloxetine, and mirtazapine. She was admitted to the psychiatric clinic for approxi-
mately a month with depression diagnosed about 2 years previously. Subsequently, her symptoms had improved. About 3 months previously, she relapsed and was admitted to the same clinic again, where she received medications including duloxetine 60 mg, mirtazapine 30 mg, escitalopram 20 mg, aripiprazole 1 mg, and quetiapine 75 mg for 2 months. However, her symptoms did not improve with the medication, and she was referred to our clinic. The depression symptoms included diminished interest, loss of energy, psychomotor agitation, weight loss, and insomnia. She reported that she was lethargic and did not want to do anything but she was not particularly depressed and had not experienced any increase in stress recently. She was admitted to our department of psychiatry for accurate assessment and treatment. The patient received a score of 26 on the Hamilton Depression Rating Scale. In addition to depressive symptoms, she had experienced cognitive impairment with gradual onset. She had a score of 22/30 on the Korean-Mini Mental State Examination, 1 on the Clinical Dementia Rating, and 4 on the Global Deterioration Scale. Her cognitive functions, including memory, executive function, and language function, were particularly impaired. In a structural brain imaging study, no degenerative changes other than a small aneurysm and internal carotid artery stenosis that had already been diagnosed were observed (Fig. 1). The results of the brain single-photon emission computed tomography for the evaluation of brain function indicated reduced perfusion in both anterior cingulate gyri (Fig. 2). She had no other medical history.

During the evaluation, we prescribed antidepressants such as fluoxetine 60 mg, venlafaxine 225 mg, mirtazapine 30 mg, and aripiprazole 5 mg, because the patient’s symptoms for depression required immediate treatment. She continued to take the medications for more than a month, but the symptoms did not improve, and she appeared to be deteriorating. In a reassessment of the patient’s medical history we focused on her apathy symptoms instead of her depression symptoms. At that point, the patient was evaluated and received a score of 72 on the Apathy Evaluation Scale (AES). This 18-item scale assesses apathy in behavioral, cognitive, and emotional domains over the previous 4 weeks. Scores range from 18 to 72, with higher scores indicating greater apathy. Subsequently, we first reduced and then discontinued all antidepressants, including SSRIs. Olanzapine and sleeping pills were continued to control her insomnia and agitation. Subsequently, she became slightly more active but this change was not sufficient. We prescribed methylphenidate and gradually increased its dosage to 25 mg. We then added modafinil 200 mg to her treatment regime. Following these changes of medication, her score on the AES improved to 35, and she continued performing her daily activities after discharge. The drugs she was taking at discharge were: methylphenidate 25 mg, modafinil 200 mg, olanzapine 10 mg, donepezil 10 mg, and aripiprazole 5 mg. As her activity levels increased a little, her daily life function improved slightly but her subjective cognitive decline continued. We will keep track of the changes in her cognitive function in the future.

**Discussion**

Apathy is a common behavioral problem that often goes undiagnosed and untreated [4]. There is considerable overlap in the clinical presentations of apathy and depression. Furthermore, apathy may be part of a cluster of negative symptoms in patients with illnesses such as schizophrenia or Alzheimer’s disease [5]. However, apathy has been demonstrated to relate, independently of these other psychiatric symptoms, to a variety of outcomes [5]. The presence of apathy is linked to deficits in the performance of activities of daily living and functional decline and can be of considerable clinical significance [4].

A common feature of many of the conditions in which apathy is prominent is the presence of lesions or other abnormalities in the frontal lobe-subcortical circuitry. Neuroimaging studies of various clinical populations have reported correlations between apathy and structural and functional changes within the frontal lobe, particularly the anterior cingulate gyrus and subregions of the basal

![Fig. 1. No degenerative changes on T2-flair image. RPF, right posterior foot.](https://doi.org/10.12701/yujm.2019.00150)
Neuropsychological studies have reported a relationship between apathy and poorer performance on tests of executive functions \([6]\). Indeed, in the present case, the patient displayed decreased function of the anterior cingulate gyri as well as deterioration of executive functions.

A recent case-control study \([7]\) reported that apathy appeared to be greater in patients who were treated with SSRI than in patients who were not. Currently, we do not have enough data to understand how altering of serotonergic signaling might cause apathy. It is biologically possible that frontal lobe dysfunction, induced by SSRIs, may be responsible for the apathy \([7]\). Conditions that can induce frontal lobe dysfunctions are often caused by imbalances of neurotransmitters in the brain. Prolonged and excessive serotonin in the synapse may lead to a decrease in the

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**Fig. 2.** Mild reduction of perfusion in anterior cingulate gyrus on brain single-photon emission computed tomography.
transmission of dopamine in the frontal lobe. High serotonin levels may also cause a decrease in acetylcholine which can induce an increase in dopamine function. A relationship between serotonin and noradrenaline is another possible mechanism [8].

If SSRI-induced apathy is detected, reduction of SSRI dose or discontinuation of SSRIs is required. When discontinuation of the SSRI is not successful, augmentation or switching to a different class of medications is helpful [2]. Apathy has been emerging as a target for pharmacotherapeutic interventions, and new trials have recently been completed [9]. Methylphenidate for the treatment of apathy has been investigated in double-blind, placebo-controlled randomized trials (RCTs), and an effect on apathy was reported [10]. The findings of these studies were consistent with other findings supporting dopaminergic dysfunction in apathy. Other catecholamine agonists that can treat the symptoms of apathy include amantadine [11], bromocriptine [12], levodopa [13], selegiline [14], and bupropion [15]. RCTs have provided evidence of the efficacy of cholinesterase inhibitors [16] and memantine [17] in the treatment of apathy in Alzheimer’s disease. Modafinil is a multimodal stimulant that increases the activity of histamine, norepinephrine, serotonin, dopamine, and orexin systems in the brain [18]. Two recent case reports [4,19] suggested its effectiveness in the treatment of apathy. Additionally, some studies have investigated the effects of olanzapine on negative symptoms, including apathy. Apathetic patients with major depressive disorder may benefit from treatment with olanzapine. In an open-label study [20] with nonpsychotic, major depressive disorder patients who were treated with SSRIs and displayed significant apathy, the addition of olanzapine in the treatment regime yielded a significant decrease on the AES.

In the present case, the apathy symptoms improved slightly but the patient continued to experience cognitive impairment. Apathy is the most common behavioral problem associated with Alzheimer’s dementia, affecting 70–90% of patients, and the presence of apathy is linked to deficits in the performance of activities of daily living and functional decline [4]. In one study, minor cognitive impairment (MCI) patients with apathy symptoms, not depressive symptoms, were diagnosed with Alzheimer’s dementia almost seven times more frequently than MCI patients without apathy symptoms. Patients with apathy should keep track of their cognitive function, taking into consideration the risk of dementia.

The growing body of empirical investigations on the neurobiology of apathy will likely prove helpful in providing a sound theoretical basis for the application of currently available treatments, as well as for the development of novel therapeutic interventions [5].

Conflicts of interest

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

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Catastrophic catecholamine-induced cardiomyopathy rescued by extracorporeal membrane oxygenation in recurrent malignant pheochromocytoma

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Pheochromocytoma (PCC) is a rare catecholamine-producing tumor with the incidence in hypertension of 0.1-0.6%. PCC crisis is an endocrine emergency that can lead to hemodynamic disturbance and organ failure such as catecholamine-induced cardiomyopathy. The circulatory collapse caused by it often requires mechanical support. The author reports an unusual case in which a patient who previously underwent surgery for malignant PCC developed catecholamine-induced cardiomyopathy, and successfully recovered using extracorporeal membrane oxygenation.

Keywords: Cardiogenic shock; Cardiomyopathy; Extracorporeal membrane oxygenation; Pheochromocytoma

Introduction

Pheochromocytoma (PCC) is a rare catecholamine-producing neuroendocrine tumor derived from chromaffin cells of the sympathetic nervous system. Because it can present with various clinical symptoms other than the classical triad of headache, palpitation and sweating, early diagnosis is not easy [1,2]. PCC crisis is a situation in which the secretion of catecholamine abruptly increases, caused by some spontaneous or specific stimuli. This is an endocrine emergency that can lead to hemodynamic disturbance and organ failure associated with significant mortality [3,4]. This situation often requires mechanical support, and some cases of effective recovery using extracorporeal membrane oxygenation (ECMO) are reported [5,6]. In a considerable number of cases, PCC is initially diagnosed due to the outbreak of a PCC crisis [3]. However, there are very few cases in which patients who have undergone surgical treatment for PCC are later diagnosed with a recurrence due to PCC crisis. Here, the author reports an unusual case in which a patient who previously underwent surgery for malignant PCC developed catecholamine-induced cardiomyopathy after taking glucocorticoids, and successfully recovered using ECMO.

Case

A 44-year-old Asian female visited the emergency room complaining of a headache, nausea and vomiting. She had visited the hospital 11 years earlier for gestational hypertension. She had been diagnosed with PCC in the right adrenal gland (Fig. 1A) and successfully treated with a right adrenalectomy. PCC of the adrenal gland scaled score had been 7, so the tumor had been diagnosed as malignant. For the first 5 years of follow-up, no signs of recurrence had been found, and she had not visited the hospital since then. Four hours before her visiting the present hospital, she took 4 mg of methylprednisolone due to urticaria. Her blood pressure (BP) was 180/100 mmHg, and other vital
signs were stable. An electrocardiogram and a chest X-ray showed normal findings. She had no history of diabetes, but her glucose level was 330 mg/dL, and bicarbonate level was reduced at 13.5 mmol/L. Other blood tests showed no abnormal findings, and urine dipstick analysis showed ketone 1+. Hydration was performed with normal saline due to the possibility of early phase diabetic ketoacidosis. Abdomen-pelvis computed tomography (CT) was performed, and there was no evidence of local recurrence of PCC (Fig. 1B).

Four hours after visiting the hospital, she complained of severe dyspnea. She showed tachycardia with a pulse of 130 beats/min, severe tachypnea with a respiratory rate of over 35 breaths/min, and a fever of 38°C. Rale was heard from both lung fields, and a chest X-ray revealed a rapidly developed bilateral consolidation (Fig. 2). Intubation and mechanical ventilation were performed because of severe hypoxemia. According to echocardiography conducted at bedside, although the cardiac chamber size was normal, there was severe global hypokinesia of the left and right ventricles. The left ventricular ejection fraction was approximately 20% and the tricuspid annular peak velocity had decreased to 6 cm/s, indicating severe ventricular dysfunction of both ventricles. Antibiotics and diuretics were used, considering the possibility of acute respiratory distress syndrome due to atypical pneumonia or acute pulmonary edema caused by heart failure. She was moved to the intensive care unit from the emergency room. Five hours after intubation, her BP was dropped to 60/30 mmHg and pulse gradually slowed. One mg of epinephrine and 1 mg of atropine were injected immediately, but asystole occurred. Cardiopulmonary resuscitation was performed immediately and venoarterial ECMO was prepared. ECMO was initiated 15 minutes after arrest. Asystole and return of circulation were repeated 3 times for 42 minutes. After that, the patient’s rhythm was restored and no further cardiac arrest occurred. She was treated for 5 days with support of ECMO, mechanical ventilation, and inotropic agents. She recovered consciousness and ECMO was removed when her vital signs became stable without inotropics. After 10 days, ventilator weaning and extubation were performed.

The results of hormone tests performed at the time of hospitalization showed an overall increase in catecholamine (Table 1), and catecholamine-induced cardiomyopathy due to PCC was strongly suspected. In order to confirm the recurrence of PCC, a 131I-metaiodobenzylguanidine (MIBG) scan was performed, but

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**Table 1. Plasma levels of catecholamines**

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>Level</th>
<th>Normal range (×10⁸/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>19,752.5</td>
<td>0-140 pg/mL</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>5,641.0</td>
<td>70-1,700 pg/mL</td>
</tr>
<tr>
<td>Metanephrine</td>
<td>46.1</td>
<td>0-0.5 nmol/L</td>
</tr>
<tr>
<td>Normetanephrine</td>
<td>23.5</td>
<td>0-0.9 nmol/L</td>
</tr>
</tbody>
</table>

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Fig. 1. (A) Abdomen-pelvis CT of 11 years ago shows a 9x7 cm sized pheochromocytoma (arrow) in the right adrenal gland. (B) There is no evidence of local recurrence on abdomen-pelvis CT at admission. CT, computed tomography.

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no focal radioactive uptake lesion was shown. The patient’s CT was reviewed closely, and a faint mass-like lesion was detected on her right sacrum. Sacrum magnetic resonance imaging was performed, and a 2.7 x 2.9 x 2.8 cm sized well-defined, lobulated, and slightly expansile mass with mainly T1 low T2 high signal intensity and heterogeneous enhancement at right upper sacral ala was seen (Fig. 3). Other small lesions, which are assumed to be metastasis, were also found at the S2 level of the sacrum, right iliac bone, and lower L4 vertebral body. A positron emission tomography scan showed an increase of uptake in the same regions (Fig. 4). For a histological verification, an open bone biopsy was performed. Atypical spindle-shaped tumor cells showing synaptophysin and chromogranin positivity were found upon histopathologic examination (Fig. 5). These results demonstrated that the lesions on the sacrum were recurrent metastatic PCC.

In the patient’s follow-up, the cardiac functions, including left and right ventricles, were found to be completely recovered, with 65% of ejection fraction. Coronary angiography performed after ventilator weaning showed no abnormal findings. Currently, her BP is being successfully regulated with an α-blocker (doxazocin) and β-blocker (carvedilol) and treatment for the recurrent PCC is planned.
cardiac functions later on such, many cases including this case show recovery of damaged most catecholamine induced cardiac injuries are reversible, and as even though the patient had suffered a cardiac arrest. Fortunately, case, the patient was effectively rescued with timely use of ECMO pump or ECMO, in effectively treating such cases ports of using mechanical support, such as intraaortic balloon treatment alone is not enough in some cases. There have been re
spasm

The key to treat PCC crisis is to recognize early and stabilize the patient’s vital sign until the causes are corrected, but medical treatment alone is not enough in some cases. There have been reports of using mechanical support, such as intraaortic balloon pump or ECMO, in effectively treating such cases. In this case, the patient was effectively rescued with timely use of ECMO even though the patient had suffered a cardiac arrest. Fortunately, most catecholamine induced cardiac injuries are reversible, and as such, many cases including this case show recovery of damaged cardiac functions later on. Therefore, if necessary, more ag-
gressive mechanical support should be considered during the unstable period of PCC crisis. It can save the patients from the vicious cycle and increases their chances for cardiac function recovery, which would ultimately increase the survival rate.

Causes of PCC crisis include trauma, surgery, and anesthesia, as well as drugs such as glucagon, radiocontrast agent, tyramine, tricyclic antidepressant, and metoclopramide. Cases occurring after glucocorticoid administration are very rare, with only about 20 cases reported to date. In this case, methylprednisolone taken prior to admission was suspicious of the cause of PCC crisis. Although it was a low dose, no other possible causes were found, and since PCC crisis also occurred in another case when 2 mg of dexamethasone was administered during dexamethasone suppression test, the possibility of 4 mg dose of methylprednisolone being the cause was believed to be sufficient enough.

Two possible mechanisms by which glucocorticoid causes PCC crisis can be considered. First, glucocorticoid promotes the production and release of catecholamines. In normal adrenal gland, the adrenal medulla is already exposed to excessive amount of glucocorticoid secreted from nearby adrenal cortex, and thus, it is not significantly affected by introduction of external glucocorticoid. However, PCC is not surrounded by the adrenal cortex and has a modified vascular structure, and as a result, it has lost the ability to regulate external steroids and overreacts to them. Glucocorticoid activates enzymes involved in catecholamine metabolism, production, and secretion in PCC, thereby promoting catecholamine secretion. Second, glucocorticoid reinforces the actions of catecholamines in the peripheral vascular tissues by suppressing the formation of endothelial-derived vasodilators such as nitric oxide and prostacyclin.

The point of interest in this case is that PCC crisis occurred in a patient who was already being treated for malignant PCC and recurrence was confirmed through such event, as well as this crisis was induced by steroids. PCC itself is not a common disease, and recurrences are very rare with only 4.6–6.5%. Poor prognosis is associated with local recurrence or distant metastasis, which often appear within the first 2 years from the initial diagnosis, but such occurrence even after 40 years has also been reported. In this case, bone metastasis might had proceeded 5 years after surgery. In the meantime, catecholamine was not being secreted in excessive amounts to cause symptoms, but catecholamine secretion did increase suddenly when steroids were taken, which is believed to have caused the PCC crisis.

In this case, we could not easily find the lesion, because there

Discussion

Classic symptoms of PCC are headache, palpitation and sweating. However, many patients show atypical symptoms and it is not difficult to find cases with PCC crisis as the first symptom. PCC crisis involves suddenly released catecholamines that act on α-adrenergic receptors to cause arterial contraction, along with reduction in intravascular effective volume, which ultimately causes cellular ischemia to have a systemic effect. It often causes cardiovascular emergencies, such as myocardial infarction, catecholamine-induced cardiomyopathy, and acute myocarditis, which eventually lead to progression of circulatory collapse. The mechanism of cardiac injury includes direct cardiac myocyte damage of catecholamine, increased myocardial oxygen demand and decreased oxygen supply due to coronary artery spasm.

The key to treat PCC crisis is to recognize early and stabilize the patient’s vital sign until the causes are corrected, but medical treatment alone is not enough in some cases. There have been reports of using mechanical support, such as intraaortic balloon pump or ECMO, in effectively treating such cases. In this case, the patient was effectively rescued with timely use of ECMO even though the patient had suffered a cardiac arrest. Fortunately, most catecholamine induced cardiac injuries are reversible, and as such, many cases including this case show recovery of damaged cardiac functions later on. Therefore, if necessary, more ag-

Fig. 4. Positron emission tomography scan shows an increase of uptake in the mass of sacrum.

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was no focal recurrence on CT and no focal radioactive uptake lesion showing on the $^{131}$I-MIBG scan. The MIBG scan is an effective functional imaging procedure for detecting PCC. Its specificity is quite high (95–100%), but the sensitivity is relatively low (approximately 77–90%). The false-negative of the MIBG scan can be affected by tumor size, drugs that interfere with iodine uptake, amount of iodine isotope used, imaging time etc. Several studies have reported that the sensitivity of the MIBG scan is higher for adrenal PCC than for extra-adrenal PCC indicating that tumor location also affects sensitivity [18]. In this case, because the recurrent lesion was a sacrum, extra-adrenal lesion, it would not have been found with an MIBG scan.

In conclusion, PCC crisis is a very serious condition that can often be life threatening, and as such, the patient needs to be treated carefully; and if necessary, mechanical support should be considered without hesitation. In addition, it can be caused by various medications, and since steroids that are commonly prescribed can also be a cause, although rare, caution should be taken when prescribing steroids. Attention should be paid not only to patients that are currently suspected of having PCC, but also patients with prior treatment history as well.

**Conflicts of interest**

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

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References

Late complication of the Nuss procedure: recurrent cardiac tamponade

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Pectus excavatum (PE) is known as one of the most common congenital deformities of the anterior chest wall. The Nuss procedure is an effective surgical therapy to correct PE. Here, we report a case of recurrent cardiac tamponade due to hemopericardium that occurred after 16 months following the Nuss procedure. The cause of recurrent hemopericardium was thought to be local, repetitive irritation of the pericardium by the Nuss steel bar. We should keep in mind that this serious complication can occur after the Nuss procedure, even in the late phase.

Keywords: Cardiac tamponade; Complication; Nuss procedure; Pectus excavatum

Introduction

Pectus excavatum (PE) is one of the most common congenital chest wall deformities, occurring in approximately 1:400 births and affecting males 5 times more often than females [1]. Patients with PE may have a variety of symptoms, such as nonspecific chest pain, shortness of breath on exertion, and psychological distress, which are the indications of surgical treatment.

There are two standard surgical therapies of PE: the Ravich procedure, corrective osteotomy, and the Nuss procedure, minimally invasive repair of PE using the Nuss bar. The Nuss procedure has become a widely used method correcting PE since Dr. Donald Nuss introduced it in 1998, with benefits including being a minimally invasive technique and having a short operative duration [2]. This procedure elevates the depressed sternum by passing a suitably shaped, concave steel bar beneath the sternum, resting on the outer aspects of the ribs on each side under thoracoscopy [3]. Pericarditis or pericardial effusions as one of the postoperative complications have been reported in 1.6–2.4% of cases [4-6], but progression to cardiac tamponade is very rare.

Here, we introduce an instructive case which gives us meaningful messages that cardiac tamponade can occur as a late complication of the Nuss procedure.

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**Case**

A 23-year-old woman visited the emergency department with the chief complaint of chest discomfort with a burning sensation on the anterior chest, aggravated by inspiration or bending forward. She was a university student majoring in vocal and got the Nuss procedure 16 months ago to correct PE for increasing lung capacity. Her blood pressure (BP) was 105/65 mmHg with a heart rate of 128 beats/min (bpm), and her respiration rate was 22 breaths/min and body temperature was 36.9°C. On physical examination, her neck veins were distended, and her lower extremities were swollen with pitting edema. Lung sounds were clear, but her heart sound was mildly decreased on auscultation. A chest X-ray showed a well-positioned Nuss bar without any pathologic finding, laboratory finding, nor any abnormalities. Electrocardiogram showed a low voltage QRS. Trans-thoracic echocardiography (TTE) revealed a moderate amount of pericardial effusion with diastolic collapse of the right ventricle, more than 25% of respiratory variation of mitral inflow velocity, expiratory diastolic hepatic vein flow reversal, and dilated inferior vena cava (IVC) with plethora, which were all compatible hemodynamic findings for cardiac tamponade (Fig. 1).

Emergent TTE and fluoroscopy-guided pericardiocentesis were performed through a subxiphoid approach, and 700 mL of bloody effusion was drained. The pericardial fluid analysis revealed exudate with a hemoglobin of 12.2 g/dL and an adenosine deaminase (ADA) of 36.7 mg/dL. Chest computed tomography (CT) was performed to rule out disorders that can cause hemopericardium, but there was no evidence of acute aortic syndrome such as aortic dissection and no abnormal malignant mass or lung infiltration. The pericardial tube was removed on hospital day 5 and follow-up echocardiography showed a nearly disap-

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**Fig. 1.** Transthoracic echocardiography findings of her first emergency department visit show a moderate amount of pericardial effusion with tamponade. (A) A moderate amount of pericardial effusion (arrowheads) with the diastolic collapse of the right ventricle (star). (B) Respiratory variation of mitral inflow exceeding 25%. (C) Expiratory diastolic hepatic vein flow reversal (arrowheads). (D) Dilated inferior vena cava with a plethora (arrow).
peared pericardial effusion.

Bloody pericardial effusion had a high ADA level and, considering the high incidence of tuberculous pericarditis in South Korea, the etiology of pericardial effusion was assumed to be tuberculous pericarditis, and anti-tuberculous medications were started on hospital day 8. The patient discharged without any further events and followed up at the outpatient department free of symptoms.

However, after 2 months, she visited our emergency department again with similar symptoms as on her first visit. Her initial vital sign showed a BP of 136/87 mmHg with a heart rate of 128 bpm, but 4 hours later, her BP abruptly decreased to 60/40 mmHg. Emergent bedside echocardiography was performed and revealed a small amount of pericardial effusion. Even though the amount was small, 2-dimensional and Doppler studies demonstrated significant tamponade physiology, including septal bouncing motion, more than 25% of the respiratory variation of mitral inflow, expiratory diastolic hepatic vein flow reversal, and dilated IVC with a plethora (Fig. 2). Considering recurrent pericardial effusion, even on the anti-tuberculous medication, we tried to find another etiology other than tuberculous pericarditis. We carefully reviewed the chest CT and recognized that the Nuss bar is contacting with the pericardium (Fig. 3). We inferred that the friction between the Nuss bar and pericardium can make hemopericardium, and it could be the main culprit of recurrent cardiac tamponade in this patient. The amount of pericardial effusion was too small to perform pericardiocentesis, and elimination of the Nuss bar was needed to prevent recurrent tamponade, so

Fig. 2. Transthoracic echocardiography findings of her second emergency department visit. Note all the tamponade physiologies are present, even with a small amount of pericardial effusion. (A) A small amount of pericardial effusion in subcostal view. (B) Respiratory variation of mitral inflow exceeding 25%. (C) Expiratory diastolic hepatic vein flow reversal (arrowheads). (D) Dilated inferior vena cava with a plethora (arrow).
we made a decision to have an emergency operation of a pericardial window formation and removal of the Nuss bar at the same time. About 200 mL of bloody pericardial effusion was drained by window formation, and the Nuss bar was successfully removed. There was no perforation or injuries to the pericardium or great vessels. Her central venous pressure decreased from 14 to 7 mmHg after the window formation, and her BP recovered to normal range.

On the fourth postoperative day, the pericardial effusion almost disappeared upon echocardiography. Interferon-gamma release assays, polymerase chain reaction testing for tuberculosis, and mycobacterial culture of pericardial fluid were all negative and anti-tuberculous medications were stopped. She discharged without any specific complications on hospital day 17, and follow-up echocardiography at 6 months did not show any abnormal findings.

**Discussion**

The Nuss procedure is one of the well-established operation techniques for correcting PE [2]. Although some authors developed a variety of sternal-lifting methods to improve the visual field and to increase the space under the substernal area minimizing the risk of cardiac injury during and after surgery [5,7], cardiac complications have occurred in real clinical fields.

In general, complications caused by the Ravitch procedure and Nuss bar implantation can be classified as acute and chronic complications, based on 30 days after the surgical procedure [8,9], and life-threatening events, such as cardiac perforation and other direct heart or aortic injuries have mostly occurred acutely during still bar placement. Pericarditis and pericardial effusion are rare complications that can develop later; however, progression to life-threatening cardiac tamponade is extremely rare [4-6]. The cases presented with tamponade were mostly related to sternal wire after the Ravitch procedure [10-12] or Nuss bar displacement injuring the ascending aorta [13] or pericardium [14].

To our best knowledge, this is the first case report of very late spontaneous cardiac tamponade, without evidence of Nuss bar displacement. In our case, there was no evidence of visible traumatic injury at great vessels and the pericardium on the chest CT scan and surgical field during a window formation of the pericardium. There was also no other foreign body or metal wire, which can cause a direct injury to the pericardium. Referring to literature from Yang et al. [14], we thought that the reason of recurrent, late-onset cardiac tamponade after the Nuss procedure is due to micro-bleeding of small vessels around the pericardium into the pericardial space caused by local, repetitive irritation of the pericardium by the Nuss steel bar. After the removal of the bar, there had been no pericardial effusions upon follow-up TTE in the outpatient clinic.

Another important instruction we learned from this case was that only 200 mL of a very small amount of pericardial effusion can cause life-threatening cardiac tamponade if it accumulates rapidly (Fig. 3). Rapidly increasing pericardial fluid first reaches the limit of the pericardial reserve volume and then quickly exceeds the limit of parietal pericardial stretch, causing a steep rise in intra-pericardial pressure, subsequently developing cardiac tamponade [15-17].

Those who have a Nuss bar or other foreign devices adjacent to the heart presenting with pericardial effusion should be considered for the possibility of hemopericardium and cardiac tamponade related to the device, and only small pericardial effusions can induce cardiac tamponade if it accumulates rapidly over the compensatory mechanism of the pericardium.

**Conflicts of interest**

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![Fig. 3. Chest computed tomography showing contact of the Nuss bar (arrowheads) and pericardium (arrows).](https://doi.org/10.12701/yujm.2019.00241)
References


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Incidentally found cystic lymphangioma of the adrenal gland in an elderly male cadaver

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Keywords: Adrenal cyst; Cadaver; Lymphangioma; Male

Introduction

Benign adrenal vascular pathologies, including tumors, cysts, and pseudocysts, are relatively rare entities that are mostly right-sided and predominantly observed in females [1]. These lesions may occur concomitantly with other adrenal tumors associated with hormone secretion. Cysts of the adrenal glands are rare and often detected incidentally during radiological examinations or at autopsy. Their reported incidence ranges 0.06–0.18% [2–4].

Adrenal cysts are classified into the following four main groups: endothelial cysts (45%), pseudocyst (39%), epithelial cysts (9%), and parasitic cysts (7%) [5]. Endothelial cysts include hemangioma and lymphangioma [6]. Adrenal cystic lymphangiomas do not exhibit pathognomonic clinical or radiological presentation. Certain features of these entities raise the suspicion of malignancy, including a heterogeneous appearance in imaging analyses, the presence of necrosis in the center of the mass accompanied by calcification, and the size of the adrenal mass [7].

We present a case of a cystic lesion on the right adrenal gland in an elderly man and discuss its common and distinct features.

Case

We found multiloculated cysts on the right adrenal gland in the cadaver of a 75-year-old Korean man, whose cause of death was pneumonia, during routine educational dissection.

An ovoid cystic mass protruded from the outer surface of the adrenal gland (Fig. 1A). Dissection revealed a multilocular cystic lesion measuring 3.3 × 3.0 cm (longest and transverse diameters in external dimension, respectively) within the adrenal gland. The cystic walls were thin, and the cavities contained a pale to tan-colored gelatinous material (Fig. 1B).
Microscopy analysis revealed that the cystic structures were surrounded by flattened adrenal parenchyma (Figs. 2A, 2B) and the inner surfaces were lined by a single layer of flattened cells with bland nuclei (Fig. 2C). The lining cells were diffusely positive for cluster of differentiation 31 (CD31) (Fig. 2D) and podoplanin (D2-40) (Fig. 2E), and negative for pan-cytokeratin (Fig. 2F). The pathological diagnosis confirmed a cystic lymphangioma arising from the adrenal gland.

**Discussion**

Lymphangiomas, benign malformations of lymphatic vessels, are most frequently noted in children aged less than 2 years [8,9]. Although the exact cause has not been established yet, these entities are generally regarded as congenital malformations in which obstruction or agenesis of lymphatic tissue results in lymphangiectasia due to a lack of normal communication within the lymphatic system [8,10]. The majority of lymphangiomas are detected in the neck, axillary region and mediastinum (95%), and the remaining 5% are found in the abdominal cavity [8,11]. Adrenal lymphangiomas account for less than 1% of all abdominal lymphangiomas [12]. To date, less than 60 adrenal lymphangioma cases have been described [13], with only 7 cases reported in Korean [14].

While lymphangiomas are typically detected in childhood and are rare in adults, adrenal lymphangiomas are predominantly noted in women in aged approximately 40 years, mostly right-sided, and unilateral (mean size 8.9 cm; range 2.0–35.0 cm). Histologically, all adrenal lymphangiomas show a typical multicystic lesion composed of irregular dilated spaces that are lined by flattened bland simple endothelial cells [12] and have potential malignancy incidence of about 4.1% [10,15]. Adrenal cystic lymphangiomas are usually asymptomatic because of their size and location [8]. The most common complaint is pain, which is localized in back, the right upper quadrant of abdomen, or is generalized as abdominal pain [10]. Transabdominal adrenalectomy is the treatment of choice. Recent recommendations entail the aspiration of material from the adrenal cysts instead of their surgical excision both for diagnosis and management, in cases where malignancy is not suspected or the lesion is non-functional and asymptomatic [6,8,10,12,16].

In conclusion, small asymptomatic adrenal cystic lymphangiomas without malignant transformation were incidentally detected in an elderly Korean male cadaver and the diagnosis was confirmed by histopathological staining for CD31 and D2-40. Unlike other adrenal cystic lymphangiomas, the adrenal lymphangioma in the present case was detected in an elderly male cadaver due to their size during postmortem investigation. Therefore, careful inspection of the adrenal cysts by clinicians and anatomists is warranted, despite the patient’s age and sex.
Fig. 2. Microscopic findings of the right-sided adrenal cystic lesion. (A) Multilocular cystic spaces are present. (B) Entrapped adrenal parenchyma (arrows) is present. (C) The cystic wall is lined by a single layer of flattened endothelial cells (arrowheads) (hematoxylin and eosin stain, ×40 [A and B] and ×200 [C]). The lining endothelial cells are positive for cluster of differentiation 31 (D) and podoplanin (E), and negative for pan-cytokeratin (F) (immunohistochemical stain, ×40 [D] and ×100 [E and F]).
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Conflicts of interest

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Isolated hemorrhage in the cerebellar vermis with vertigo and body lateropulsion to the contralesional side

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Introduction

Hemorrhage in the cerebellar vermis represents only 5% of all cases of cerebellar hemorrhage [1], which can easily rupture into the fourth ventricle through its roof and frequently extends into the pontine tegmentum. Prognosis of patients with hemorrhage in the cerebellar vermis is worse than that for overall cerebellar hemorrhages. Thus, cases of patients with a small hematoma in the cerebellar vermis, who present with clinical features of labyrinthine disorder without any other additional neurological deficits suggestive of a cerebellar lesion, are extremely rare, with only few reported in the literature [2-4]. We report a case of isolated hematoma in the vermis in a patient who presented with vertigo, ipsilesional nystagmus, and body lateropulsion to the contralesional side as the sole clinical manifestation.

Case

A 64-year-old woman with hypertension and hypercholesterolemia presented to the emergency department with acute onset of severe non-positional vertigo accompanied by nausea, vomiting, and postural imbalance. Three days before presentation, she had experienced mild vertigo with nausea after sauna bathing, which improved with bed rest. At first, the patient had rotational vertigo aggravated by head motion and change of position. The following morning, her vertigo gradually worsened and persisted regardless of posture, until she eventually lost the ability to maintain even a sitting posture due to severe vertigo and disequilibrium. She had no other posterior circulation symptoms, such as diplopia, slurred speech, limb clumsiness or weakness, sensory loss, tinnitus, or hearing loss. A bedside neurological examination revealed a spontaneous right beating horizontal nystagmus with a torsional component in the primary position and upon gaze to the right or left. A bedside head impulse test was negative. There was no periodic alternating nystagmus. She had no skew deviation or head tilt and also showed no ophthalmoaresis, dysmetria, hypotonia, limb ataxia, or loss of proprioception. She fell to the left side when at...
tempting to stand with her eyes open. All neurological findings suggested peripheral vestibulopathy, except the normal head impulse test finding. Brain computed tomography (CT) showed a subtle, small high-density region in the right cerebellum posterior to the fourth ventricle (Fig. 1). Brain magnetic resonance imaging (MRI) showed a small, acute stage hematoma selectively involving the nodulus of the right cerebellum located immediately posterior to the fourth ventricle with mild edema of the surrounding brain tissue (Fig. 2). Findings of brain magnetic resonance angiography (MRA) were unremarkable.

Severe vertigo, vomiting, and staggering gait continued for 1 week after admission. Thereafter, her symptoms gradually resolved, and she could walk without assistance after 2 weeks. Two months after presentation, she had no further dizziness or gait disturbance.

Discussion

There have been several reports of patients with isolated lesions of the cerebellar vermis presenting with clinical features similar to those of peripheral vestibulopathy without the usual signs or symptoms of cerebellar dysfunction, such as dysmetria, ataxia, asymmetrical pursuit and/or optokinetic nystagmus, and dysarthria [5-9]. The patterns of presenting signs and symptoms differ among patients depending on the location of the lesions. Isolated infarction of the nodulus can cause vertigo, nausea, vomiting, ipsilesional nystagmus, and body lateropulsion to the contralesional side and may, therefore, be clinically misdiagnosed as a labyrinthine disorder, which was previously reported as “pseudo-vestibular neuritis” syndrome [5,6].

Cases of periodic alternating nystagmus, body lateropulsion, positional vertigo and nystagmus, pursuit eye movement disorders, or gait ataxia caused by lesions in various locations or different pathologies of the vermis have been reported [7-9]. Small cerebellar hemorrhage presenting with features similar to those of labyrinthine disorders has only been reported in a few cases, and not in the Korean literature [2-4]. In our case, T1-weighted gradient echo imaging showed a small hematoma in the caudal part of the lingula and the adjacent inferior-posterior white matter, immediately posterior to the fourth ventricle, in the right cerebellar vermis. This lesion caused acute vertigo, ipsilesional nystagmus, and body lateropulsion to the contralesional side. Isolated body lateropulsion can occur as a result of brain lesions at various locations, including the thalamus, cerebellum, medulla oblongata, and midbrain [5-7,10-14].

In the cerebellum, lesions of the nodulus, rostral vermis, tonsil, or cerebellar peduncle can develop isolated body lateropulsion [5-7,9-11]. Body lateropulsion is contralesional in patients with lesions in the nodulus [5,6], but ipsilesional in patients with lesions in the cerebellar peduncle, dorsal spinocerebellar tract, or rostral vermis [7,10-14]. However, our patient had lateropulsion to the contralesional side, ipsilesional nystagmus, and vertigo, which may be attributed to the location of the hematoma, which involved not only the lingula but also part of the nodulus and the white matter adjacent to the lingula. Spontaneous nystagmus and body lateropulsion in the nodulus lesion could be explained by disruption of nodular inhibition over the ipsilateral vestibular nuclei. The nodular Purkinje cell projects to the areas in the inferior vestibular nucleus, and a lesion in the nodulus may disinhibit the ipsilateral inferior vestibular nucleus, resulting in body lateropulsion to the contralateral side and ipsilateral spontaneous nystagmus [5].

The physician regarded the lesion as an artifact on the initial brain CT, due to the very small hematoma size and subtle high-density of the lesion. Our patient presented with vertigo, ipsilesional nystagmus, and postural imbalance, with no additional signs or symptoms of cerebellar or brain stem dysfunction. However, brain MRI and MRA were performed to rule out a central vestibular lesion as the patient had vascular risk factors, such as hypertension, hypercholesterolemia, and old age. Caudal cerebellar infarction has been reported as the cause of isolated acute vertigo lasting for >48 hours in one-fourth of elderly patients who showed no abnormality on neurological examination, except for

Fig. 1. Brain computed tomography image shows a high-density subtle, small region (arrow) in the vermis of the right cerebellum, posterior to the fourth ventricle.
nystagmus. Therefore, brain MRI should be performed to differentiate cerebellar infarction from vestibular neuritis, especially in elderly patients with vascular risk factors [15]. Brain MRI clearly showed a small, acute stage hematoma in our case and is very helpful in patients with small hematomas restricted to the vermis, which may not be visible on brain CT. We concluded that the etiology of the hemorrhage in our case was spontaneous and hypertensive because the patient had no history of recent head trauma and vascular anomaly on MRI and MRA, and furthermore, the coagulation system was normal.

In summary, we report the case of a patient with small, isolated hemorrhage in the cerebellar vermis who presented with acute

Fig. 2. Brain magnetic resonance imaging. Axial and sagittal fluid-attenuated inversion recovery imaging (A, B) and T₂-weighted gradient echo imaging (C, D) show a small, isolated, acute stage hematoma (arrow) selectively involving the vermis of the right cerebellum located immediately posterior to the fourth ventricle, with mild edema of the surrounding brain tissue.

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vertigo and body lateropulsion to the contralesional side. We believe that elderly patients, especially those with vascular risk factors, need to be examined carefully and brain MRI should be performed to rule out the possibility of a cerebellar lesion, even though patients present with signs and symptoms suggestive of acute peripheral vestibulopathy. MRI allows for the accurate detection of even small, isolated hematomas or infarctions located in the cerebellar vermis.

Conflicts of interest

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

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Massive cerebral venous sinus thrombosis secondary to Graves’ disease

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Cerebral venous sinus thrombosis (CVT) is a rare cerebrovascular condition accounting for 0.5–1% of all types of strokes in the general population. Hyperthyroidism is associated with procoagulant and antifibrinolytic activity, thereby precipitating a hypercoagulable state that predisposes to CVT. We report the case of a 31-year-old Korean man with massive CVT and diagnosis of concomitant Graves’ disease at admission. Early diagnosis and prompt treatment of CVT are important to improve prognosis; therefore, CVT should be considered in the differential diagnosis in all patients with hyperthyroidism presenting with neurological symptoms.

Keywords: Graves’ disease; Hyperthyroidism; Intracranial thrombosis; Thyrotoxicosis

Introduction

Cerebral venous sinus thrombosis (CVT) is often categorized as a distinct subgroup of cerebrovascular disease, showing an estimated incidence of 0.5–1% of all kinds of strokes in the general population [1]. CVT is associated with various conditions that result in a hypercoagulable state. Hyperthyroidism is a predisposing factor in approximately 1.7% of patients with CVT [2]. Notably, 23 papers (including 11 case reports) have discussed the association between thyrotoxicosis and CVT; however, few studies have investigated the pathophysiology of this condition or established a definitive association because of methodological limitations. We describe a patient who presented with massive CVT associated with venous infarction in the right frontal lobe and diagnosis of concomitant Graves’ disease.

Case

A 31-year-old Korean man visited the Emergency Department at Dongsan Hospital with fainting spells and convulsive movements. He reported a several-day history of recurrent headaches with vomiting, as well as a several-month history of weight loss and heat intolerance. He also reported a history of appendectomy in 1994, short-term use of medications for suspected major depressive disorder in 2012, and surgery for shoulder fracture in 2014.

Initial laboratory investigations revealed normal blood counts, as well as kidney and liver function. Initial brain computed tomography (CT) revealed no definitive evidence of intracranial hemorrhage or detectable low-density infarct-like lesions. Electrocardiography revealed sinus tachycardia. The patient’s symptoms worsened the day following his initial visit. Thyroid function tests revealed a serum thyroid-stimulating hormone (TSH) level < 0.01 µU/mL, free thyroxine 4.73 ng/dL, and tri-iodothyronine 378.45 ng/dL. Laboratory tests performed for the assessment of a hypercoagulable state revealed the following results: anti-thyroid peroxidase (anti-TPO) 18.34 IU/mL, thyroglobulin antibody (Ab) within normal limits, TSH-receptor Ab 14.14 IU/L, d-dimer 5.74 µg/mL, fibrinogen 554.5 mg/dL, and factor VIII 210.6%.

Brain magnetic resonance imaging (MRI) was performed based on the emergency protocol followed at our hospital, includ-
ing a sagittal T1-weighted image (T1WI), diffusion-weighted image (DWI), T2 fluid-attenuated inversion recovery (FLAIR) and T2* gradient recalled echo (GRE) sequences. It revealed focal hemorrhagic infarction in the right frontal lobe with venous thrombosis in the superior sagittal (Figs. 1A, 1B) and the right transverse (Fig. 1C) and sigmoid sinuses (not shown in the figure). Indeed, the initial brain CT revealed a subtle hyperdensity lesion on non-enhanced CT images and filling defects in the affected venous sinuses on contrast-enhanced images, particularly partial CVT of the superior sagittal sinus with a contrast-outlined triangular filling defect (empty delta sign) (Figs. 1D–1F). However, these findings were missed during the initial evaluation of images. The patient developed left-sided weakness 3 days after his initial visit. Additional brain CT and MR venography revealed an increased thrombus burden, presenting as significant filling defects in the superior sagittal and the right transverse and sigmoid sinuses (Fig. 2). Previous focal hemorrhagic infarction remained stable without progression, and no additional infarct core or hemorrhagic focus was identified. He received anticoagulation therapy with low-molecular-weight heparin (clexane 60 mg twice a day) on the same day. His left-sided weakness disappeared 3 days after treatment initiation, and headache and nausea also improved 2 days thereafter.

Work-up including thyroid ultrasonography, thyroid scan with

![Fig. 1. Initial contrast-enhanced brain CT and MR scans. Focal hemorrhagic infarction is present in the right frontal lobe (asterisk) and a dark signal intensity representing a thrombus (blooming artifact) is present in the superior sagittal sinus (arrows) on the MR scan obtained the following day (A, FLAIR; B, T2* GRE sequences). A similar dark signal intensity representing a thrombus (arrow) is also present in the right transverse sinus (C, T2* GRE). These findings were neglected on the previous CT scan. The right transverse sinus shows a subtle hyperdensity (arrowhead) on a non-enhanced axial CT scan (D). Contrast-enhanced axial CT scans (E, F) show corresponding filling defect (arrowhead) at the same location and a partial empty delta sign (arrowhead) in the superior sagittal sinus, which were missed during evaluation of the initial brain CT scan. CT, computed tomography; MR, magnetic resonance; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo.](https://doi.org/10.12701/yujm.2019.00339)
technetium-99m, and laboratory tests confirmed a diagnosis of Graves’ disease, and methimazole (antithyroid agent categorized as a TPO inhibitor) was administered at a dose of 12.5 mg twice a day along with indenol (beta blocker) at a dose of 10 mg three times a day. Normalization of thyroid function tests was observed following this treatment.

Follow-up contrast-enhanced CT and MR venography were performed with additional sequences (DWI, T2-FLAIR, T2* GRE) to evaluate residual venous thromboses, 27 days after the patient’s initial visit. These imaging studies revealed a significantly reduced thrombus burden in the cerebral deep venous sinuses and partially restored flow enhancement in the right transverse sinus.

**Fig. 2.** Brain CT and MR venography scans obtained on admission (3 days after the initial brain CT). Axial non-enhanced CT scan (A) shows a more prominent hyperdensity (HU 70) in the right transverse sinus (arrowhead), which shows the same density (HU 70) on contrast-enhanced brain CT scan (B). Absence of flow-related enhancement is present in the superior sagittal and right transverse to sigmoid sinuses, as opposed to normal flow-related enhancement observed in the left transverse sinus (arrowhead) on an MIP image (C). Sagittal reconstructed MR venography scan (D) shows the propagation of the filling defect along the superior sagittal sinus (arrows). CT, computed tomography; MR, magnetic resonance; HU, Hounsfield units; MIP, maximum intensity projection.
and sigmoid sinuses without complete recanalization (Fig. 3). At the time of his outpatient follow-up the following month, physical and laboratory examination did not reveal any abnormal neurological findings, and he maintained a euthyroid state. Conventional MR and CT angiography performed at his 1-year follow-up confirmed near-complete recanalization of the superior sagittal and the right transverse and right sigmoid sinus (Fig. 4).

Fig. 3. Conventional and sagittal reformatted MR venography scans obtained at 1-month follow-up. Reduced thrombus burden in the superior sagittal sinus (arrows) is present on axial FLAIR sequence (A), T2* GRE sequence (B), contrast-enhanced T1WI (C), and sagittal reformatted MR venography scan (D). MR, magnetic resonance; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; T1WI, T1-weighted image.
Discussion

CVT is categorized as a distinct subgroup of cerebrovascular disease, showing an incidence of approximately 0.5–1% of all kinds of strokes in the general population [1]. CVT is associated with various conditions that result in a hypercoagulable state. Hyperthyroidism is implicated as a predisposing factor for CVT because hyperthyroidism is known to cause elevated procoagulant levels.

Fig. 4. Conventional MR and delayed-phase CT angiography scans obtained at the last follow-up showing near-complete recanalization of the cerebral venous sinuses. Conventional MR venography scan (A, FLAIR; B, T2* GRE; and C, contrast-enhanced T1WI) and delayed-phase CT angiography scan (D) obtained at 1-year follow-up shows near-complete recanalization of the superior sagittal and the right transverse and sigmoid sinuses (arrows). MR, magnetic resonance; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; GRE, gradient recalled echo; T1WI, T1-weighted image.
in the vascular hemostatic system leading to a hypercoagulable state. However, to date only several small studies have directly investigated the association between hyperthyroidism and CVT. Diagnostic radiological findings in patients with CVT include the following: venous sinus thrombosis can be identified as a hyperdensity lesion of the affected sinus for the first 7–14 days on non-enhanced CT images. Following contrast administration, CVT presents as a filling defect in a sinus, and patients with involvement of the sagittal sinus typically show the ‘empty delta sign.’ Reportedly, CT venography shows a sensitivity of 95% in these cases. MRI can help in visualization of the clot as well as the sequela. The clot shows variable signal intensity based on its stage (acute-to-chronic stage). During the acute stage, the clot appears isointense on T1WI and hypointense on T2WI, and during the subacute stage the clot appears as a hyperintense lesion on T1WI. Notably, clots can be easily detected as a dark signal within areas of hemorrhage (typically described as blooming artifacts) on T2* GRE or susceptibility images. Venous infarction can be identified on DWI. Contrast-enhanced MR or MR venography shows greater sensitivity in detecting thrombosis, which presents as a venous filling defect in patients with CVT.

The patient described in this case report presented with massive CVT without a medical history to support this diagnosis. Diagnosis of Graves’ disease concomitant with CVT was established only at the time of his current admission. The association between CVT and thyrotoxicosis was first described by Kaliebe in 1913 [3] and by Doyle in 1927 [4]; 23 cases have been reported thereafter [5-8]. A hypercoagulable state induced by high circulating levels of thyroid hormones is the likely mechanism contributing to the pathophysiology in these cases [9]. High levels of thyroid hormones increase blood levels of coagulation factors and inhibit fibrinolyis. Notably, increased levels of fibrinogen, von Willebrand factor, coagulation factors VIII, IX and X, and plasminogen activator inhibitor-1 shorten the activated partial thromboplastin time and prolong the clot lysis time [10]. The combined effects of hyperthyroidism on procoagulant and fibrinolytic activity increase the risk of venous thrombosis. Bensalah et al. reported that increased Factor VIII levels were observed in 10 of 26 patients with CVT and concomitant thyrotoxicosis [9]. In our case, the factor VIII level was 210.6%. Currently, venous thrombosis is accepted as a ‘multicausal’ disease because several genetic and environmental conditions work together [11].

Although initial laboratory investigations revealed poorly controlled thyroid hormone levels indicating thyrotoxicosis, the diagnosis of CVT was delayed in this patient until confirmatory MR venography was performed, because we initially missed the partial empty delta sign in the affected cerebral venous sinuses. Any further delay in diagnosis could have led to irreversible neurological injury even with optimal treatment. This case emphasizes the importance of careful evaluation for early diagnosis of venous thrombosis in young adults with hyperthyroidism presenting with unexplained neurological symptoms. Clinicians should be aware that further evaluation to confirm CVT should be considered with CT or MR angiography with venous phase and blood-sensitive MR sequences, such as T2* GRE or susceptibility weighted imaging in patients with a suspicious hyperdensity or the empty delta sign in the cerebral venous sinuses on brain CT.

In conclusion, previously published data strongly suggest that hyperthyroidism should be considered an important risk factor for CVT. Comprehensive evaluation is warranted for prompt diagnosis of CVT in patients with hyperthyroidism presenting with unexplained neurological symptoms.

Conflicts of interest

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

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Peer review process

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Manuscript preparation

Review article

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