The preventive effects of perioperative oral care on surgical site infections after pancreatic cancer surgery: a retrospective study

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Abstract

Purpose Pancreatic ductal adenocarcinoma (PDAC) is the most malignant cancer of the gastrointestinal system, and is associated with high rates of postoperative complications, including surgical site infections (SSIs). Perioperative oral care is an effective measure for preventing postoperative pneumonia. However, the preventive effects of perioperative oral care on SSIs have not been reported. We investigated the preventive effects of perioperative oral care on SSIs after pancreatic cancer surgery.

Methods A total of 103 patients with PDAC who underwent radical resection at Hiroshima Prefectural Hospital (2011–2018) were enrolled in this retrospective study. Of the 103 patients, 75 received perioperative oral care by dentists and dental hygienists (oral care group), whereas 28 did not (control group). Univariate and multivariate analyses with propensity score as a covariate were used to investigate the incidence and risk factors of SSIs in the oral care and control groups.

Results The incidence of SSIs was significantly lower in the oral care group than in the control group (12.0% vs. 39.3%, \( P = 0.004 \)). Logistic regression analysis revealed that a soft pancreas, the surgical procedure (pancreaticoduodenectomy), blood transfusion, diabetes mellitus, and the absence of oral care intervention were risk factors for SSIs. The odds ratio for the absence of oral care intervention was 6.090 (95% confidence interval: 1.750–21.200, \( P = 0.004 \)).

Conclusion Our results suggest that perioperative oral care may reduce the risk of developing SSIs after pancreatic cancer surgery. These findings need to be evaluated in future prospective studies.

Trial registration UMIN registration number: UMIN000042082; October 15, 2020, retrospectively registered.

Keywords Distal pancreatectomy · Pancreatic cancer · Pancreaticoduodenectomy · Perioperative oral care · Perioperative oral management · Surgical site infection

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most malignant cancer of the gastrointestinal system, and its prevalence is increasing worldwide [1, 2]. Despite improvements in multimodal approaches, the overall survival rate remains low at approximately 10% [3]. Although surgical resection offers the greatest likelihood of a cure, it is a complex and invasive surgical procedure that is associated with a high incidence of postoperative complications [4]. Surgical site infections (SSIs) are the most common postoperative complication following pancreatic resection. Early adjuvant chemotherapy is warranted in most patients. However, delayed treatment initiation in patients with SSIs increases the risk of cancer recurrence and decreases long-term survival [5]. In addition, increased length of postoperative hospitalization and medical costs due to SSIs are of significant
concern. Therefore, the development of preventive measures against SSIs is a critical challenge to be resolved in modern cancer surgery. In this regard, SSI prevention guidelines recommend effective SSI prevention measures throughout the preoperative and postoperative periods [6, 7].

Perioperative oral care is an infection prevention measure that has demonstrated efficacy for preventing postoperative pneumonia [8–10] and SSIs after head and neck cancer surgery [11]. However, there is a paucity of reports on the preventive effects of perioperative oral care on postoperative SSIs in gastrointestinal surgery [12, 13], and the preventive effects of this measure on pancreatic cancer have not been reported to date. In 2011, we introduced perioperative oral care with dental intervention into the perioperative multidisciplinary management of pancreatic surgery, and gradually started referring patients to the hospital’s dentistry department. The aim of this study was to investigate the preventive effects of perioperative oral care on the incidence of SSIs after pancreatic cancer surgery.

Materials and methods

Participants

This was a single-center retrospective study based on patient records. Patients who underwent pancreatic cancer surgery with curative intent at Hiroshima Prefectural Hospital between February 1, 2011, and December 31, 2018, were initially enrolled. Patients with PDAC were included. Patients with other pancreatic malignancies or those who underwent laparoscopic surgery and/or total pancreatectomy were excluded. After the exclusion of ineligible cases, 103 patients were finally enrolled. Of the 103 enrolled patients, 75 received perioperative oral care by dentists and dental hygienists, whereas 28 did not (Table 1).

Surgical procedures

Skin preparation was performed using povidone-iodine solution unless contraindicated. If contraindications were present, chlorhexidine was used. An impervious plastic wound protector was applied after laparotomy in all patients. Surgical procedures that were performed included pancreaticoduodenectomy (PD), distal pancreatectomy (DP), and standard lymphadenectomy. PD included pylorus-preserving PD (PPPD), subtotal stomach-preserving PD (SSPPD), and classic PD (Whipple procedure). All surgeries were either performed by or performed under the supervision of the same surgeon (YM).

Before closing the surgical incision, the surgeon replaced their gloves and the abdominal cavity was flushed with 10 L of saline solution. Abdominal drains (BLAKE DRAINS®, 19 Fr, Ethicon Inc., Somerville, NJ, USA) were placed

| Characteristic               | Oral care group n = 75 | Control group n = 28 | P-value |
|-----------------------------|------------------------|----------------------|---------|
| Age (years)                 | 70.4 ± 8.7             | 64.6 ± 10.0          | 0.012*  |
| Sex (male/female)           | 41/34                  | 16/12                | 1       |
| Body mass index (kg/m²)     | 22.3 ± 3.2             | 23.0 ± 3.3           | 0.129   |
| Preoperative serum albumin (g/dL) | 3.8 ± 0.4             | 4.0 ± 0.4            | 0.002** |
| Preoperative CRP (mg/dL)    | 0.7 ± 1.5              | 0.5 ± 0.9            | 0.946   |
| Diabetes mellitus           | 26 (34.7)              | 8 (28.6)             | 0.642   |
| Ischemic heart disease      | 6 (8.0)                | 1 (3.6)              | 0.671   |
| Preoperative biliary drainage| 29 (38.7)              | 12 (42.9)            | 0.822   |
| Surgical procedure (PD/DP)  | 45/30                  | 20/8                 | 0.361   |
| Operation time (min)        | 438.5 ± 196.9          | 478.5 ± 155.9        | 0.195   |
| Blood loss (mL)             | 484.2 ± 399.9          | 870.6 ± 635.1        | 0.001** |
| Blood transfusion           | 8 (10.7)               | 7 (25.0)             | 0.112   |
| Vascular resection          | 24 (32.0)              | 9 (32.1)             | 1       |
| Pancreatic texture (firm/soft)| 30/45                  | 13/15                | 0.655   |
| Onset of clear fluid intake (POD) | 1.1 ± 0.2             | 1.2 ± 0.5            | 0.043*  |
| Onset of solid food intake (POD) | 3.4 ± 2.6             | 4.4 ± 1.0            | <0.001***|
| Mobilization (POD)          | 2.4 ± 1.4              | 3.7 ± 1.5            | <0.001***|

Values are expressed as means ± standard deviations or as numbers (%)

*P < 0.05, **P < 0.01, ***P < 0.001

CRP, C-reactive protein; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; POD, postoperative day
around the pancreaticojejunostomy site or remnant pancreatic stump. Pancreatic juice was drained through an internal lost-stent or trans-jejunal external drainage tube. A needle-catheter-jejunostomy (Jejunostomy Catheter, 9 Fr, Nippon Covidien Inc.) was inserted in patients undergoing PD.

The abdominal fascia was closed with continuous double loop closure using monofilament absorbable sutures (PDS® II, ETHICON, Inc., Somerville, NJ, USA). The subcuticular layer was created using monofilament absorbable sutures (PDS® PLUS, ETHICON, Inc., Somerville, NJ, USA) after irrigation of the subcutaneous tissue space with 1 L of saline. Finally, the skin was closed using surgical tape. The nasogastric tube was removed at the end of surgery.

**Perioperative management**

Oral immunonutrition (IMPACT®, Nestle Health Science, Japan) was provided according to a protocol of 3 packs/day (250 kcal/pack) until 2013 and 4 packs/day (110 kcal/pack: revised products by Nestle Health Science) from 2014 for 7 days prior to surgery. Because the product specifications were revised in 2014, we adjusted the omega-3 fatty acid and arginine content to ensure equality between the periods before and after 2014.

An enhanced recovery after surgery (ERAS) program was implemented for all patients undergoing PD and for patients undergoing DP from 2014. Prolonged fasting from midnight and mechanical bowel preparation on the day before surgery were not undertaken in all cases. The following postoperative ERAS elements were provided: onset of clear fluid intake on postoperative day (POD) 1 in all patients and solid food intake on POD 2 in patients undergoing DP or on POD 3 in patients undergoing PD. Enteral nutrition in patients undergoing PD was provided until POD 7. With regard to the mobilization schedule, the goal was set to walk around the ward without assistance from POD 3.

All patients received intravenous (IV) prophylactic antibiotic therapy, with cefmetazole (1.0 g) for patients undergoing DP or cefozopran hydrochloride (1.0 g) for patients undergoing PD. IV therapy was commenced from just before skin incision and repeated at 3-h intervals throughout the operation, followed by every 8 h until POD 2. The surgical incision was covered with a sterile dressing until POD 2. The insertion sites of the drainage tube were sealed with a moisture-permeable sterile film until tube removal and were removed by POD 5.

From 2011 to 2013, patients undergoing DP (n = 10) were managed using traditional procedures of care. Preoperative fasting from midnight, mechanical bowel preparation, and IV fluid administration on the day before surgery were routinely performed. The onset of drinking clear fluid was planned after passing through the flatus. Solid food intake, mobilization, and drain removal were performed at the discretion of the surgeon.

**Perioperative oral care interventions**

Seventy-five patients in the oral care group received oral care by dentists and dental hygienists at the hospital. The first oral care session was performed in the outpatient clinic 2 weeks before surgery in conjunction with other multidisciplinary programs, including nutritional guidance, pharmaceutical management, and rehabilitation. The second session was performed the day before surgery. The third session was performed at bedside on POD 1. Subsequent sessions were performed 2–10 days after surgery.

Oral care comprised professional procedures such as scaling, mechanical tooth cleaning, removal of tongue coating, cleaning of dentures, adjustment of ill-fitting dentures, and extraction of infected teeth, as well as instructions on oral self-care. Self-care instructions encompassed the use of toothbrushes, interdental brushes, dental floss, denture brushes, tongue brushes, and mouthwash. In addition, participants were advised to perform oral self-care upon waking and before each meal to reduce the ingestion of oral bacteria.

On the other hand, 28 patients were not referred to the hospital’s dentistry department and did not receive professional management or oral self-care instructions.

**Variables**

All data were retrieved from the electronic database of Hiroshima Prefectural Hospital and the medical records of the Information Management Agency. The following variables were examined to compare the risk of SSIs between the oral care and control groups: age, sex, body mass index (BMI), comorbidities (diabetes mellitus and ischemic heart disease), preoperative blood test data (albumin and C-reactive protein [CRP]), preoperative biliary drainage, surgical procedure (PD and DP), operation time, estimated blood loss, intraoperative blood transfusion, concomitant vascular resection, pancreatic texture (firm or soft), SSI (incisional or organ/space), pneumonia, bacteremia, postoperative pancreatic fistula (POPF), onset of clear fluid intake, onset of solid food intake, completion of postoperative mobilization, and postoperative hospital stay.

SSI was defined according to the Centers for Disease Control and Prevention guidelines [6] for SSI prevention. We limited our analysis to clinically significant SSIs of Clavien-Dindo grade II [14] or higher. POPF was defined according to the severity classification guidelines of the International Society for Pancreatic Surgery (ISGPS) [15]. We limited our analysis to clinically significant grade B and C POPFs. Mobilization was considered complete when patients were...
able to walk at least one lap (85 m) of the ward corridor without assistance.

Statistical analysis

Statistical analysis was performed using EZR software version 1.52 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Data are expressed as means ± standard deviations or as numbers (percentages). Categorical variables and proportions were compared using Fisher’s exact test. Continuous variables were compared using the Mann–Whitney U test. The level of statistical significance was set at a two-tailed P-value < 0.05.

The incidence of postoperative complications (including SSIs) and postoperative hospital stay in the oral care and control groups was evaluated using univariate analysis. In order to reduce selection bias in the retrospective data, we calculated the propensity score for each patient using the following 17 variables: age, sex, BMI, albumin, CRP, diabetes mellitus, ischemic heart disease, preoperative biliary drainage, surgical procedure, operation time, blood loss, blood transfusion, concomitant vascular resection, pancreatic texture, onset of clear fluid intake, onset of solid food intake, and completion of mobilization. The propensity score was used as a covariate, and multivariate logistic regression analysis with backward stepwise selection (exclusion criteria, P < 0.1) was used to evaluate risk factors for SSIs.

Ethical considerations

Due to the retrospective nature of the study, the requirement for informed consent was waived by the Institutional Review Board. The research protocol was published, and the opportunity to opt out was guaranteed. The study was approved by the Institutional Review Board of Hiroshima Prefectural Hospital (approval number: 201712–13). Research was conducted in accordance with the 1964 Helsinki Declaration and its later amendments. The study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (registration number: UMIN000042082).

Results

Patients

The demographic characteristics of patients in the oral care (n = 75) and control groups (n = 28) are presented in Table 1. Compared to the control group, the oral care group had a higher mean age (P = 0.012), lower serum albumin levels (P = 0.002), less estimated blood loss (P = 0.001), earlier start date of drinking clear fluid (P = 0.043), earlier start date of solid food intake (P < 0.001), and earlier completion of mobilization (P < 0.001). No significant between-group differences were observed in the other parameters.

Outcomes

SSIs occurred in 20 of 103 patients (19.4%); incisional SSIs occurred in four patients and organ/space SSIs occurred in 18 patients (two overlapping cases). SSIs occurred in 9 (12.0%) of 75 patients in the oral care group and 11 (39.3%) of 28 patients in the control group. The incidence of SSIs was significantly lower in the oral care group than in the control group (P = 0.004). The mean postoperative hospital stay was significantly shorter in the oral care group than in the control group (P < 0.001) (Table 2).

The incidence of postoperative pneumonia, bacteremia, and POPF in the oral care and control groups was 1.3% and 3.6% (P = 0.472), 1.3% and 7.1% (P = 0.179), and 8.0% and 0.083

Table 2 Incidence of postoperative complications and length of hospital stay in the oral care and control groups

| Variable                        | Oral care group n = 75 | Control group n = 28 | P-value |
|---------------------------------|------------------------|----------------------|---------|
| Postoperative complication      |                        |                      |         |
| Pneumonia                       | 1 (1.3)                | 1 (3.6)              | 0.472   |
| Bacteremia                      | 1 (1.3)                | 2 (7.1)              | 0.179   |
| POPF                            | 6 (8.0)                | 6 (21.4)             | 0.083   |
| SSI                             | 9 (12)                 | 11 (39.3)            | 0.004** |
| Incisional SSI                  | 2 (2.7)                | 2 (7.1)              | 0.297   |
| Organ/space SSI                 | 7 (9.3)                | 11 (39.3)            | <0.001***|
| Length of postoperative hospitalization (days) | 20.4±9.5              | 33.5±16.2            | <0.001***|

Values are expressed as means ± standard deviations or as numbers (%)

**P < 0.01, ***P < 0.001

POPF, postoperative pancreatic fistula; SSI, surgical site infection
21.4% ($P=0.083$), respectively, with no significant differences observed between the groups (Table 2).

Univariate analysis revealed a soft pancreas ($P=0.042$) and the absence of oral care intervention ($P=0.004$) as significant risk factors for SSIs. The results of the multivariate analysis adjusted using the propensity score as a covariate indicated that diabetes mellitus, the surgical procedure (PD), intraoperative blood transfusion, a soft pancreas, and the absence of oral care intervention were significant risk factors associated with SSIs. The odds ratio for the absence of oral care intervention was 6.090 (95% confidence interval: 1.750–21.200, $P=0.004$) (Table 3).

**Discussion**

Recent advancements in surgical techniques, surgical instruments, adjuvant chemotherapy [16], and perioperative management, such as the ERAS program [17], have improved the outcomes of gastrointestinal surgery. Nevertheless, the incidence of infectious complications, such as SSIs, has not been significantly attenuated despite the introduction of ERAS programs [18]. The incidence of perioperative complications, including SSIs, is higher in PDAC surgery than in other gastrointestinal surgeries [19]. In this study, we investigated the preventive effects of perioperative oral care on the incidence of postoperative SSIs in patients with PDAC. We observed that perioperative oral care for PDAC significantly reduced the incidence of SSIs in the univariate analysis. Notably, multivariate analysis revealed that the absence of oral care intervention was an independent risk factor for SSIs, in addition to, a soft pancreas, the surgical procedure (PD), diabetes mellitus, and intraoperative blood transfusion. A soft pancreas is a major risk factor for POPF [20] and has a higher likelihood of progressing to organ/space SSIs. Compared to DP, PD is a more complex and invasive procedure, and patients undergoing PD have a higher risk of biliary tract infections and SSIs [21]. Diabetes mellitus is a well-known risk factor for postoperative infections [22], and blood transfusion has also been reported as a risk factor for postoperative SSIs in pancreatic cancer [23]. Therefore, our findings suggest that, in addition to previously reported risk factors for SSIs in PDAC, the absence of oral care intervention is a novel independent risk factor for SSIs.

**Table 3** Univariate and multivariate analyses of risk factors for SSIs after adjustment for propensity scores

| Variable                      | SSIs         | Univariate | Multivariate |
|-------------------------------|--------------|------------|--------------|
|                               | (+)          | (-)        | $P$-value    | OR     | 95% CI      | $P$-value |
| Age (years)                  |              |            |              |        |             |           |
| $(\geq 70)$                  | 8 (40.0)     | 45 (54.2)  | 0.321        | –      | –           | –         |
| Sex                          |              |            |              |        |             |           |
| (Male)                       | 14 (70.0)    | 43 (51.8)  | 0.210        | –      | –           | –         |
| Body mass index (kg/m$^2$)   |              |            |              |        |             |           |
| $(\geq 24)$                  | 6 (30.0)     | 26 (31.3)  | 1            | –      | –           | –         |
| Preoperative serum albumin (g/dL) |   |            |              |        |             |           |
| $(\geq 3.8)$                 | 14 (70.0)    | 46 (55.4)  | 0.314        | –      | –           | –         |
| Preoperative CRP (mg/dL)     |              |            |              |        |             |           |
| $(\geq 0.2)$                 | 7 (35.0)     | 27 (32.5)  | 1            | –      | –           | –         |
| Diabetes mellitus (Present)  |              |            |              |        |             |           |
| Ischemic heart disease (Present) | 9 (45.0)     | 25 (30.1)  | 0.289        | 2.950  | 0.832–10.500| 0.094     |
| Preoperative biliary drainage (Present) | 1 (5.0)     | 6 (7.2)    | 1            | –      | –           | –         |
| Surgical procedure (PD)      |              |            |              |        |             |           |
| Operation time (min) $(\geq 450)$ | 11 (55.0)    | 39 (47.0)  | 0.621        | –      | –           | –         |
| Blood loss (mL) $(\geq 500)$ | 11 (55.0)    | 32 (38.6)  | 0.212        | –      | –           | –         |
| Blood transfusion (Present)  |              |            |              |        |             |           |
| Vascular resection (Present) |              |            |              |        |             |           |
| Pancreatic texture (Soft)    |              |            |              |        |             |           |
| Onset of clear fluid intake $(\geq $POD 2) | 1 (5.0)     | 8 (9.6)    | 1            | –      | –           | –         |
| Onset of solid food intake $(\geq$ POD 4) | 11 (55.0)    | 35 (42.2)  | 0.326        | –      | –           | –         |
| Mobilization $(\geq$ POD 4)  | 5 (25.0)     | 17 (20.5)  | 0.762        | –      | –           | –         |
| Oral care intervention (Absent) | 11 (55.0)    | 17 (20.5)  | 0.004**      | 6.090  | 1.750–21.200| 0.004**   |

Values are expressed as numbers (%)

$^*$ $P < 0.05$, $^{**} P < 0.01$, $^{***} P < 0.001$

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; PD, pancreaticoduodenectomy; POD, postoperative day; SSI, surgical site infection
In this study, perioperative oral care did not significantly reduce the incidence of pneumonia and bacteremia, which are infectious complications distinct to SSIs. The lower incidence of pneumonia and bacteremia compared to that of SSIs, and a previous report [24], may have obscured any differences. Future studies should investigate the preventive effects of perioperative oral care on the incidence of pneumonia and bacteremia using larger sample sizes.

Michaud et al. [25] indicated five routes of bacterial dissemination from the oral cavity to the pancreas, namely the general circulation, lymphatic system, duodenum, biliary duct, and bacterial translocation (BT) from the intestinal tract. More advanced periodontal disease is associated with a greater risk of transient bacteremia and endotoxemia during chewing movements and tooth brushing [26, 27]. In addition, periodontal pathogens, such as Porphyromonas gingivalis, have been detected in 8–17% of submandibular and submental lymph nodes [28]. Alverdy et al. [29] proposed that pathogenic microorganisms present in the oral cavity and intestinal tract are taken up by neutrophils and macrophages and transported to the surgical site, causing SSIs (Trojan Horse hypothesis). This mechanism may at least partly underpin the preventive effects of perioperative oral care on SSIs during major surgeries [29]. These reports suggest that, although the oral cavity (a hotbed of periodontal disease) is part of the same gastrointestinal tract as the gut, it is equally or even more prone to BT than the gut. We conjecture that perioperative oral care reduced BT from the oral cavity by decreasing the number of bacteria in the periodontal pockets and attenuating inflammation of the periodontal tissues, which in turn reduced the occurrence of SSIs.

Another possible mechanism is that controlling the number of bacteria that enter the gastrointestinal tract from the oral cavity via saliva may contribute to SSI prevention. Humans swallow 1.0–1.5 L of saliva per day, and patients with severe periodontitis swallow 10^{12}–10^{13} oral bacteria per day [30]. During the perioperative period in pancreatic surgery, anti-acid agents, such as proton pump inhibitors, are often administered to prevent anastomotic ulcers. Fasting also decreases gastric juice secretion and weakens bactericidal effects. In patients with obstructive jaundice or postoperative external biliary drainage, the bactericidal effects of bile may be absent. In addition, oral bacteria exert cooperative protection via interspecies bacterial co-aggregation [31]. Swallowing oral pathogenic bacteria can disrupt the gut microbiome, and in fact, the gut microbiome of patients with periodontal disease has been reported to be less diverse than that of healthy individuals [32]. In animal models, oral administration of Porphyromonas gingivalis induced changes in the gut microbiome (dysbiosis), which resulted in decreased mucosal barrier function and BT [30]. In this study, perioperative oral care may have inhibited the transfer of pathogenic bacteria from the oral cavity to the intestinal tract, thereby reducing intestinal dysbiosis and BT from the intestinal tract, which in turn decreased the incidence of SSIs. In summary, it is suggested that perioperative oral care may contribute to the prevention of SSIs by reducing translocation of bacteria of both oral and gut origins.

We previously reported that perioperative oral care is effective for preventing SSIs after colorectal cancer surgery [12]. In the present study, we observed similar results for PDAC in patients with colorectal cancer. Preoperative remote site infections (urinary tract or respiratory infections) are risk factors for SSIs, and preoperative treatment is recommended [33]. Although the incidence of periodontal disease is higher than those of urinary tract and respiratory infections, the importance of preoperative remote infections in the oral cavity is commonly overlooked. Unlike antimicrobial prophylaxis, oral care does not promote opportunistic infection or antimicrobial resistance. Oral care can be easily integrated into perioperative multidisciplinary team medicine, such as the ERAS program. Therefore, while oral care may be introduced to perioperative management protocols in the future as a safe and effective infection prevention strategy, it needs to be evaluated in prospective studies.

This study has several limitations. First, this was a retrospective observational study. Information on the number of remaining teeth and the condition of periodontal tissues was unavailable in the control group; therefore, we were unable to investigate the associations between these factors and SSIs. Second, we were unable to examine the direct effects of oral care on intestinal microbiome, because we did not have the relevant data.

In conclusion, our results suggest that perioperative oral care may reduce the risk of developing SSIs after pancreatic cancer surgery. These findings need to be evaluated in future prospective studies.

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Author contribution Conceptualization: Hiroshi Nobuhara and Yasuhiro Matsugu; data curation: Hiroshi Nobuhara, Yasuhiro Matsugu, and Keiko Ito; formal analysis: Junko Tanaka and Tomoyuki Akita; investigation: Hiroshi Nobuhara, Yasuhiro Matsugu Y, and Keiko Ito; writing — original draft preparation: Hiroshi Nobuhara; writing — review and editing: Hiroshi Nobuhara and Yasuhiro Matsugu. All authors read and approved the final manuscript.

Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Code availability Not applicable.
Consent to participate  The requirement for written informed consent was waived owing to the retrospective nature of the study.

Consent to publish  Not applicable.

Conflict of interest  The authors declare no competing interests.

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