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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 tract, 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 oral care intervention was 0.164 (95% confidence interval: 0.047–0.571; $P = 0.004$).

Conclusion: Perioperative oral care reduced the risk of developing SSIs after pancreatic cancer surgery. Our findings indicate that perioperative oral care is a safe and effective infection prevention strategy that should be implemented in future perioperative management.

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

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most malignant cancer of the gastrointestinal tract, 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 in the perioperative multidisciplinary management of pancreatic surgery. Therefore, 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-centre 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).

Table 1 Demographic characteristics of the oral care and control groups

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/m^2)	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)	0.112
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***
Mobilisation (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.

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 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) programme 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 regards to the mobilisation 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 cefzopran 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, mobilisation, and drain removal were performed at the discretion of the surgeon.

Perioperative oral care interventions

Patients in the oral care group received oral care by dentists and dental hygienists. The first oral care session was performed in the outpatient clinic 2 weeks before surgery in conjunction with other multidisciplinary programmes, 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 instructions in oral self-care, scaling, professional mechanical tooth cleaning, removal of tongue coating, cleaning of dentures, adjustment of ill-fitting dentures, and extraction of infected teeth. 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.

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 ischaemic 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, bacteraemia, postoperative pancreatic fistula (POPF), onset of clear fluid intake, onset of solid food intake, completion of postoperative mobilisation, 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. Mobilisation 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 were 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, ischaemic 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 mobilisation. 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 mobilisation ($P < 0.001$). 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).

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	2 (2.7)	2 (7.1)	0.297
Organ/space	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.			

The incidence of postoperative pneumonia, bacteraemia, 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 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 oral care intervention was 0.164 (95% confidence interval: 0.047–0.571; P = 0.004) (Table 3).

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

Variable		**SSI**					
		(+)	**(−)**	**Univariate**	**Multivariate**		
		n = 20	**n = 83**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age (years)	(≥ 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)	(≥ 24)	6 (30.0)	26 (31.3)	1	–	–	–
Preoperative serum albumin (g/dL)	(≥ 3.8)	14 (70.0)	46 (55.4)	0.314	–	–	–
Preoperative CRP (mg/dL)	(≥ 0.2)	7 (35.0)	27 (32.5)	1	–	–	–
Diabetes mellitus	(present)	9 (45.0)	25 (30.1)	0.289	2.950	0.832–10.500	0.094
Ischemic heart disease	(present)	1 (5.0)	6 (7.2)	1	–	–	–
Preoperative biliary drainage	(present)	8 (40.0)	33 (39.8)	1	–	–	–
Surgical procedure	(PD)	14 (70.0)	51 (61.4)	0.608	6.010	1.440–25.100	0.014*
Operation time (min)	(≥ 450)	11 (55.0)	39 (47.0)	0.621	–	–	–
Blood loss (mL)	(≥ 500)	11 (55.0)	32 (38.6)	0.212	–	–	–
Blood transfusion	(present)	6 (30.0)	9 (10.8)	0.070	3.680	0.830–16.300	0.086
Vascular resection	(present)	7 (35.0)	26 (31.3)	0.793	–	–	–
Pancreatic texture	(soft)	16 (80.0)	44 (53.0)	0.042*	16.800	3.290–86.100	< 0.001***

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.

Variable		SSI					
		(+)	(−)	Univariate	Multivariate		
		n = 20	n = 83	*P*-value	OR	95% CI	*P*-value
Onset of clear fluid intake	(≥ POD 2)	1 (5.0)	8 (9.6)	1	–	–	–
Onset of solid food intake	(≥ POD 4)	11 (55.0)	35 (42.2)	0.326	–	–	–
Mobilisation	(≥ POD 4)	5 (25.0)	17 (20.5)	0.762	–	–	–
Oral care intervention	(present)	9 (45.0)	66 (79.5)	0.004**	0.164	0.047–0.571	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.

Discussion

Recent advancements in surgical techniques, surgical instruments, adjuvant chemotherapy [16], and perioperative management, such as the ERAS programme [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 an ERAS programme [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 and that poor oral hygiene was a risk factor for SSIs. Notably, multivariate analysis revealed that the absence of oral care intervention was a 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.

Our analysis revealed that perioperative oral care did not significantly reduce the incidence of pneumonia and bacteraemia, which are infectious complications distinct to SSIs. The lower incidence of pneumonia and bacteraemia 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 bacteraemia 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. Similar to the intestinal tract, the oral cavity acts as a reservoir of pathogenic microorganisms that cause systemic infections [26]. Oral bacteria, predominantly periodontal pathogens, adversely affect systemic diseases, such as cardiovascular disease, diabetes mellitus, rheumatoid arthritis, pneumonia, adverse pregnancy outcomes, and carcinogenesis [27, 28].

More advanced periodontal disease is associated with a greater risk of transient bacteraemia and endotoxemia during chewing movements and tooth brushing [29, 30]. In patients with severe periodontal disease, endotoxin activity in the blood during mastication is several times higher than that before mastication [30]. In addition, periodontal pathogens, such as *Porphyromonas gingivalis*, have been detected in 8–17% of submandibular and submental lymph nodes without cancer cell infiltration during head and neck cancer surgery [31]. Alverdy *et al.* [32] 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 [32]. 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.

Alternatively, 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 [33]. 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 [34], and the elderly are particularly susceptible to the transfer of oral bacteria to the intestine [35]. Therefore, periodontal disease may disrupt the intestinal microbiome. Indeed, the gut microbiome of patients with periodontal disease has been reported to be less diverse than that of healthy individuals [36]. Low microbiome diversity may decrease mucosal barrier function. In animal models, oral administration of *Porphyromonas gingivalis* induced changes in the gut microbiota (dysbiosis), which resulted in decreased mucosal barrier function and BT [33]. 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.

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. We speculate that perioperative oral care contributes to the prevention of SSIs by reducing intestinal- and oral-derived BT. Preoperative remote site infections (urinary tract or respiratory infections) are risk factors for SSIs, and preoperative treatment is recommended [37]. 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 programme. We, therefore, believe that perioperative oral care is a safe and effective infection prevention strategy that should be implemented in future perioperative management.

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; 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. Third, given that perioperative oral care has been covered by insurance in Japan since 2012, conducting a randomised controlled trial would be challenging. Therefore, multicentre retrospective cohort studies should be performed to investigate the relationship between oral care and SSIs.

In conclusion, our results suggest that perioperative oral care reduces the risk of developing SSIs after pancreatic cancer surgery. Our findings indicate that oral care is a safe perioperative infection prevention measure with no adverse events and should be incorporated in perioperative management. Future multicentre clinical trials are warranted to verify these results in a larger number of patients.

Declarations

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Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964

Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Hiroshima Prefectural Hospital (Date April 22, 2019. No. 201712-13).

Consent to participate: The requirement for written informed consent was waived owing to the retrospective nature of the study.

Consent to publish: Not applicable.

Availability of data and material: 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.

Authors' contributions: Conceptualisation: 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.

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