International Journal of Clinical Oncology (2019) 24:1081–1088
https://doi.org/10.1007/s10147-019-01446-6

ORIGINAL ARTICLE

Laparoscopic radical cystectomy in octogenarians: analysis of a Japanese multicenter cohort

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Received: 10 January 2019 / Accepted: 5 April 2019 / Published online: 10 April 2019

Abstract

Backgrounds This study aimed to describe the morbidity and mortality in older patients undergoing laparoscopic radical cystectomy (LRC) and compare the outcomes of LRC between octogenarians and younger patients (< 80 years) in a Japanese multicenter cohort.

Methods We identified 433 patients (80 octogenarians) who underwent LRC in a retrospective multicenter database from 10 institutions. The perioperative outcomes and the 90-day and late (> 90-day) complications according to the Clavien–Dindo classification were compared between the octogenarians and younger patients. Recurrence-free survival (RFS), overall survival (OS), and cancer-specific survival (CSS) were measured by the Kaplan–Meier method.

Results Compared with the younger group, the octogenarian group included a significantly higher proportion of women, patients with a lower body mass index, patients with a lower preoperative albumin level, and patients with a history of abdominal surgery. The 90-day rates of all complications and major complications (grades III–V) were 50.0% and 20.0% among octogenarians and 54.7% and 16.4% among younger patients. The 90-day mortality rate among octogenarians was 3.8%. The 2-year RFS, CSS, and OS rates for octogenarians stratified by pathological stage was 95.2, 100, and 100% for ≤ pT1; 50.7, 76.6, and 56.1% for pT2; 33.6, 82.5, and 72.6% for ≥ pT3; and 23.1, 42.2, and 37.5% for pN + or distant metastasis, respectively. There was significant difference between octogenarians and younger patients only in 2-year OS for pT2 (56.1% vs 87.7%, $p = 0.03$).

Conclusions This study revealed that LRC can be performed for selected octogenarians with a complication rate similar to that of younger patients. Appropriate risk evaluation and modification of surgical procedures are necessary for octogenarians.

Keywords Bladder cancer · Complication · Laparoscopy · Radical cystectomy · Elderly · Octogenarians

Introduction

Bladder cancer (BC) is a common urological malignancy in patients of advanced age, with the highest incidence in people aged 75–84 years [1]. Because life expectancy in developed countries is continuously rising, it is important to optimize treatment outcomes for older patients with BC.

Radical cystectomy (RC) is the reference standard for muscle-invasive BC and recurrent high-grade BC [2]. Although RC has been shown to be relatively safe in the older population, it is associated with high rates of morbidity and mortality [3–9].

Laparoscopic RC (LRC) has been described as a minimally invasive procedure with minimal blood loss, a short hospital stay, and early recovery of bowel function [10–12]. Older patients may also benefit from LRC. However, the

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10147-019-01446-6) contains supplementary material, which is available to authorized users.

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clinical outcomes of LRC for the older population, especially for octogenarians, remain unclear [13–15].

In the present study, we assessed morbidity and mortality in older patients undergoing LRC and compared the outcomes between octogenarians and younger (< 80-year-old) patients.

Materials and methods

Patients

In this institutional review board-approved study (R1581, approved in June, 2018), we retrospectively analyzed 433 patients with BC who underwent LRC from March 2008 to March 2018 at 3 academic centers and 7 satellite hospitals. The main indications for LRC were muscle-invasive BC ($n = 301$), non-muscle-invasive BC that could not be controlled with Bacillus Calmette-Guerin therapy or transurethral resection ($n = 122$), and palliative cystectomy for metastatic BC ($n = 7$) and contracted bladders ($n = 3$) after Bacillus Calmette-Guerin therapy. The selection of open RC or LRC, type of urinary diversion, extent of pelvic lymph node dissection (PLND), performance of urethrectomy, and performance of neoadjuvant/adjuvant chemotherapy were dependent upon each institution's strategy.

All patients underwent a routine laboratory examination, computed tomography scan of the chest/abdomen to evaluate distant metastasis, and pelvic magnetic resonance imaging for local staging. All patients were graded according to the American Society of Anesthesiologists (ASA) classification system. The Charlson comorbidity index (CCI) was also recorded.

The preoperative parameters evaluated in this study were age, sex, body mass index, preoperative albumin level, abdominal surgery history, ASA status, and CCI. The intraoperative variables were the operative time, estimated blood loss, organ injury, transfusion, and conversion. Perioperative outcomes such as time to oral intake and length of hospital stay after surgery were assessed. Ninety-day and late (> 90-day) complications were classified according to the modified Clavien system [16].

Analysis method

Propensity score matching was performed to control for patient characteristics and medical comorbidities that may contribute to the surgical outcomes. Propensity score was calculated with logistic regression based on preoperative parameters. Matching was performed in a one-to-one fashion, caliper of 0.2 and without replacement. Missing data were completed using a multiple imputations method.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for *R* (The *R* Foundation for Statistical Computing, version 2.13.0) [17]. It is also a modified version of *R* commander (version 1.6–3), which includes statistical functions for biostatistics.

Fisher's exact test, Student's *t* test, and the Wilcoxon signed-rank test were used for comparison of categorical, parametric, and nonparametric data. Logistic regression was used for multivariate analysis predicting 90-day complications. Recurrence-free survival (RFS), overall survival (OS), and cancer-specific survival (CSS) were assessed using the Kaplan–Meier method with the log-rank test. All tests were two-sided, and $p < 0.05$ was considered to indicate statistical significance.

Results

The patients' preoperative, intraoperative, and postoperative characteristics are shown in Table 1. Eighty of the 433 patients were octogenarians. The median age of the octogenarians was 83 years (interquartile range 81–85 years). The proportion of female patients was significantly higher among the octogenarians than younger patients. The octogenarians had a significantly lower body mass index, lower preoperative albumin level, and higher frequency of a history of abdominal surgery than younger patients.

The octogenarians underwent percutaneous ureterostomy more frequently than younger patients (50.0% vs. 15.0%, respectively; $p < 0.01$), and none underwent neobladder diversion. Intracorporeal urinary diversion was performed in 6.3% of the octogenarians and 17.6% of the younger patients. PLND and urethrectomy were performed significantly less frequently in 57.5% versus 87.8% ($p < 0.01$) and 42.5% versus 63.2% ($p < 0.01$), respectively. The median operative time was significantly shorter (475 vs. 590 min, $p < 0.01$) and the median estimated blood loss volume was significantly smaller (428 vs. 600 ml, $p = 0.049$) in the octogenarians. The open conversion rate (6.3% vs. 4.2%, $p = 0.56$) was not significantly different between the two groups.

Postoperative complications are shown in Table 2. Forty (50.0%) octogenarians and 193 (54.7%) younger patients developed 53 and 268 complications, respectively, within 90 days. The most common complications were intestinal obstruction (18.8% vs. 17.8%, $p = 0.87$) and pyelonephritis (12.5% vs. 15.8%, $p = 0.50$). Genitourinary complications were observed significantly more often in the younger group than in the octogenarians (7.9% vs. 1.3%, respectively; $p = 0.03$). There were no significant differences in other complications.

After propensity score matching all preexisting differences between the octogenarians and younger were resolved

Table 1 Patient characteristics

	Octogenarian $n=80$	Younger $n=353$	p value
Sex			
Male	50 (62.5)	285 (80.7)	<0.01†
Female	30 (37.5)	68 (19.3)	
Age, years	83 (81–85)	70 (63–75)	–
Body mass index, kg/m^2	21.6 (19.2–23.3)	22.5 (20.1–24.9)	<0.01†
ASA score			
ASA 1	18 (22.5)	123 (34.8)	0.09
ASA 2	51 (63.7)	193 (54.7)	
ASA 3	11 (13.8)	37 (10.5)	
Charlson comorbidity index	1 (1–2)	1 (0–2)	0.41
Albumin level, g/L	3.9 ± 0.4	4.1 ± 0.4	<0.01†
History of abdominal surgery	29 (36.2)	81 (22.9)	0.02†
Neoadjuvant therapy	11 (13.8)	162 (45.9)	<0.01†
Indication			
Muscle-invasive tumor	50 (62.5)	253 (71.6)	0.24
Non-muscle-invasive tumor	28 (35.0)	92 (26.1)	
Palliation	2 (2.5)	8 (2.3)	
Urinary diversion			
No	1 (1.2)	14 (4.0)	<0.01†
Cutaneous ureterostomy	40 (50.0)	53 (15.0)	
Ileal conduit	39 (48.8)	253 (71.7)	
Ileal neobladder	0 (0.0)	33 (9.3)	
Intracorporeal ileal conduit	5 (6.3)	62 (17.6)	<0.01†
Lymphadenectomy	46 (57.5)	313 (87.8)	<0.01†
Urethrectomy	34 (42.5)	223 (63.2)	<0.01†
Nephroureterectomy	7 (8.8)	38 (10.8)	0.69
Operative time, min	475 (411.5–601.3)	590 (483–687)	<0.01†
Estimated blood loss, ml	428 (221.3–1020)	600 (335–1180)	0.049†
Intraoperative complications			
Vascular injury	0 (0.0)	6 (1.7)	0.60
Nerve insure	1 (1.2)	2 (0.6)	0.46
Bowel injury	3 (3.8)	9 (2.5)	0.47
Open conversion	5 (6.3)	15 (4.2)	0.39
Transfusion	31 (38.8)	118 (33.4)	0.37
Time to oral intake, days	2 (1–3)	2 (1–3)	0.70
Hospital stay after surgery, days	36 (28.8–48)	33 (26–44)	0.07

Data are presented as n (%), median (interquartile range), or mean ± standard deviation

ASA American Society of Anesthesiologists

†$p<0.05$

(Supplementary Table 1). In the matched cohort, there were no significant difference in 90-day all and major complication rate.

The multivariate logistic regression with preoperative factors showed that inclusion in the octogenarian group was not associated with 90-day all complications (odds ratio 0.70; 95% confidence interval 0.36–1.37; $p=0.30$) or major complications (odds ratio 0.74; 95% confidence interval 0.30–1.78; $p=0.49$). Instead, a high CCI was the significant risk factor for 90-day all complications (odds ratio 1.27; 95% confidence interval 1.06–1.52; $p<0.01$) and major complications (odds ratio 1.27; 95% confidence interval 1.05–1.54; $p=0.02$). Estimated blood loss of ≥ 600 g was also a significant predictor of 90-day all complications, but not major complications (Table 3).

Three (3.8%) octogenarians and five (1.4%) younger patients died within 90 days after surgery. Among them, one octogenarian and two younger patients died of cancer progression. One octogenarian died of sepsis of unknown origin, and another died of coronary artery disease. The

Table 2 Postoperative 90-day and late (> 90-day) complications

	Octogenarian $n=80$		Younger $n=353$		p value	
	All	Major (grade ≥ III)	All	Major (grade ≥ III)	All	Major (grade ≥ III)
90-day complications						
Total, sum	53	24	268	106	0.09	1.00
Total, patient	40	16	193	58	0.46	0.51
Gastrointestinal	22	12	71	47	0.17	0.72
Infectious	14	2	97	25	0.07	0.20
Wound	2	2	27	8	0.14	1.00
Genitourinary	1	1	28	11	0.03†	0.70
Cardiac	3	2	6	3	0.22	0.23
Pulmonary	2	0	5	1	0.62	1.00
Bleeding	0	0	5	2	0.59	1.00
Thromboembolic	0	0	5	2	0.59	1.00
Neurological	2	0	5	0	0.62	1.00
Miscellaneous	4	2	10	2	0.30	0.16
Surgical	4	3	9	5	0.27	0.17
Late (> 90-day) complications						
Total, sum	14	5	76	41	0.54	0.23
Total, patient	14	5	65	35	1.00	0.40
Gastrointestinal	4	1	16	6	0.77	1.00
Infectious	3	0	13	2	1.00	1.00
Wound	3	3	12	9	0.75	0.47
Genitourinary	1	1	25	19	0.06	0.14
Cardiac	0	0	0	0	1.00	1.00
Pulmonary	1	0	0	0	0.19	1.00
Bleeding	0	0	0	0	1.00	1.00
Thromboembolic	1	0	2	0	0.46	1.00
Neurological	0	0	0	0	1.00	1.00
Miscellaneous	0	0	1	0	1.00	1.00
Surgical	1	0	7	5	1.00	0.59

†$p < 0.05$

Table 3 Multivariate analysis for predictive factors of 90-day all and major complications

Factor	90-day all complications		90-day major (grade ≥ III) complications	
	Odds ratio (95% confidence interval)	p value	Odds ratio (95% confidence interval)	p value
Preoperative variables				
Age (octogenarians vs. < 80 years)	0.70 (0.36–1.37)	0.30	0.74 (0.30–1.78)	0.49
Sex (male vs. female)	0.91 (0.49–1.69)	0.76	1.30 (0.56–3.01)	0.55
Body mass index (continuous)	1.00 (0.93–1.06)	0.90	1.04 (0.96–1.12)	0.34
Charlson comorbidity index (continuous)	1.27 (1.06–1.52)	< 0.01†	1.27 (1.05–1.54)	0.02†
Preoperative albumin (continuous)	0.89 (0.49–1.60)	0.69	0.91 (0.44–1.88)	0.79
History of abdominal surgery (yes vs. no)	0.84 (0.49–1.46)	0.54	1.65 (0.85–3.20)	0.14
Intraoperative variables				
Urinary diversion (continence vs. not)	2.42 (0.60–9.81)	0.22	1.95 (0.51–7.50)	0.33
Bleeding (≥ 600 vs. < 600 g)	2.19 (1.24–3.88)	< 0.01†	1.55 (0.75–3.19)	0.23
Operative time (every 100 min)	0.94 (0.77–1.14)	0.52	0.94 (0.74–1.19)	0.60

†$p < 0.05$

characteristics of the patients who experienced perioperative death are shown in Supplementary Table 2.

Pathological outcomes are shown in Supplementary Table 3. The histological subtype was urothelial carcinoma in most patients of both groups. At the final specimen analysis, the pathological T stage of the octogenarians was pT0, pTa/is/1, pT2, and pT3/pT4 in 8 (10.0%), 19 (23.8%), 23 (28.8%), and 30 (37.5%) patients, respectively. Of patients who underwent PLND ($n = 47$), 12 (15%) had positive nodes. A positive surgical margin was observed in 5 (6.3%) octogenarians and 19 (5.4%) younger patients.

The median follow-up duration was 17.3 months for the octogenarians. During follow-up, 26 patients (32.5%) developed tumor recurrence and 15 (18.8%) died of BC. Nine patients (11.3%) died of other diseases. The 2-year RFS, CSS, and OS rates for octogenarians stratified by pathological stage was 95.2, 100, and 100% for ≤ pT1; 50.7, 76.6, and 56.1% for pT2; 33.6, 82.5, and 72.6% for ≥ pT3; and 23.1, 42.2, and 37.5% for pN + or distant metastasis, respectively (Fig. 1a–c). There were significant differences between octogenarians and younger patients in only OS for pT2 (56.1% vs 87.7%, $p = 0.03$) (supplementary Table 4).

Discussion

In this study, LRC had a similar rate of intraoperative and postoperative complications between octogenarians and younger patients. Our results suggest that LRC can be applied to octogenarians in selected cases with certain level of safety.

The rates of all complications and major complication in the octogenarians were 50.0% and 20.0%, respectively, in this study. To the best of our knowledge, this is the first report to describe the morbidity of LRC in octogenarians. Previous studies have shown that the rates of all complications and major complications of LRC in older patients ranged from 68.0 to 89.7% and from 10.3 to 29.0%, respectively, with older patients defined as those exceeding 70 or 75 years of age [13–15]. Our data are consistent with these findings. The 90-day mortality rate in our older patients was 3.8% for all-cause death and 2.5% for other than cancer-related death. These results are also within the range of previous data (0%–14%). Moreover, in recent large series of > 200 patients aged ≥ 80 years undergoing RC, the 90-day mortality rate ranged from 13 to 15% [18–20]. Compared with these data, LRC can be performed with certain level of safety for selected octogenarians.

The complication rates were similar between older and younger patients in our study. Previous studies with an age cutoff of ≥ 70 or 75 years also showed the same conclusion [13, 15]. Among open RC series, a large single-institution study of patients aged > 80 years ($n = 117$) also revealed a comparable rate of minor complications (55% vs. 50%) and major complications (17% vs. 13%) compared with younger patients [21]. However, another nationwide study of 1605 older patients showed that after propensity score matching, the rates of homologous blood transfusions (34.2% vs. 28.7%), postoperative complications (35.9% vs. 31.5%), and in-hospital mortality (4.6% vs. 2.6%) were significantly higher in older than younger patients [3]. Despite these conflicting results, all authors emphasized that high chronological age alone is not a contraindication for surgery. Appropriate risk evaluation and patient selection are necessary for patients of advanced age.

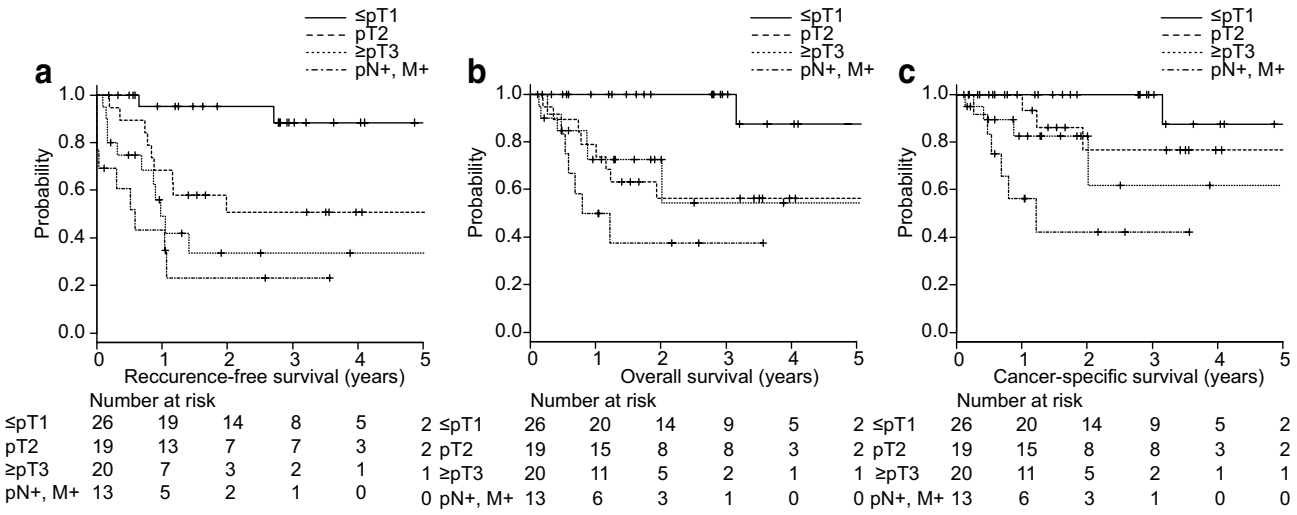

Fig. 1 Patient survival (**a**) Recurrence-free survival, (**b**) overall survival, and (**c**) cancer-specific survival for the octogenarians stratified by pathological stage

In the present study, not inclusion in the octogenarian group but a high CCI was the significant predictor of 90-day all and major complications. The CCI has been widely studied as an independent prognostic factor for perioperative mortality or long-term survival [22, 23]. The guidelines established by the European Urological Association also recommend assessing comorbidity using a validated score such as the CCI when making decisions regarding RC in older patients [2]. Older patients usually have several comorbidities, and special care is necessary for these patients. In this study, the octogenarians group had higher proportion of female, lower body mass index and lower preoperative albumin level even though octogenarians with few comorbidities were generally selected. Increased age might be associated with these differences. Female are more likely to be diagnosed as bladder cancer in elderly [24]. Loss of weight or malnutrition is a kind of frailty syndrome which is highly related to aging [25]. The importance of the perioperative nutritional status has also been reported. A low preoperative albumin level is associated with impaired wound healing and a higher rate of complications [26, 27]. A history of abdominal surgery, a history of radiotherapy, and the presence of extravesical disease are also associated with perioperative morbidity [28]. A longer operative time and greater blood loss are also known risk factors for complications [27]. Although our multivariate analysis revealed no significant association except for estimated blood loss, physicians might have tried to reduce the operative time and adopt a less invasive diversion for patients with a high risk of complications, thus introducing bias. In this study, genitourinary complications were significantly less observed in the octogenarians, due to the less frequency of urinary leakage or anastomotic stricture. The octogenarians underwent percutaneous ureterostomy more frequently, which would be associated with the difference. In addition, percutaneous ureterostomy with continuous indwelling ureter catheter was not considered as complication in this study. Therefore, for older patients with fragility or the above-mentioned risk factors, a less invasive surgical procedure (e.g., omission of lymphadenectomy or urethrectomy, application of ureterostomy instead of an ileal conduit or neobladder) might be considered.

After a median follow-up of 17.3 months, 61.3% of the older patients in our study survived without tumor recurrence. Notably, however, the RFS in patients with ≥ pT2 BC was worrisome. The 2-year RFS after LRC as reported by Albissini et al. was 91% for ≤ pT1, 82% for pT2, 60% for pT3, and 34% for pT4 [29]. A low rate of neoadjuvant chemotherapy or the performance of compromised surgical procedures such as omission of PLND or urethrectomy may affect the outcomes. According to the current guideline, PLND should be performed for all patients undergoing RC [2], but PLND for older patients is sometimes omitted because the complication rates are expected to be higher [30, 31]. Neoadjuvant chemotherapy has also been shown to have a survival benefit [32, 33]. However, these trials included few patients aged > 80 years, and the benefit of neoadjuvant chemotherapy for patients of advanced age is still unknown. Older patients are sometimes ineligible for cisplatin-based chemotherapy because of impaired renal function or a poor clinical condition. Careful patient selection is necessary to balance the benefits and risks of PLND or neoadjuvant chemotherapy for octogenarians.

In summary, we propose that octogenarians with BC who are otherwise healthy and have a low tumor burden are good candidates for LRC. Such patients in our study had a low complication rate and favorable survival outcome. In contrast, patients with a high tumor burden usually require more aggressive procedures. Considering that our study showed poor survival outcomes for octogenarians with muscle-invasive BC, LRC should be performed with caution in these patients. For older patients with more complicated conditions, the main role of RC is local control to relieve symptoms such as pain, bleeding or urinary retention. Because minimal invasiveness of LRC as evidenced by the low blood loss volume and short bowel recovery was achieved in both octogenarians and younger patients, LRC may be offered for these older patients who should avoid transfusions or a long postoperative fasting period. Nevertheless, treatment decisions for older patients should be based not only on the patients' age and tumor stage but also on their health status and social circumstances. A comprehensive geriatric assessment is a common protocol to assess such patients' functional status, comorbidities, social support, and nutritional status [34]. Ideally, all octogenarians would undergo such a geriatric assessment prior to decision-making and the formulation of a tailored plan of care.

In April 2018, the Japanese public health-care system included coverage for robot-assisted RC (RARC). Thus, minimally invasive RC may shift from LRC to RARC in Japan. Although limited studies have shown comparable outcomes of RARC for octogenarians [35, 36], high economic costs and limited institutions to perform RARC are large barriers. Further study should be necessary to compare the outcomes and costs between LRC and RARC for elderly population.

This study had several limitations. First, the number of octogenarians was relatively small and background characteristic between octogenarians and younger patients was different. Larger scaled study such as nationwide survey is necessary to identify the best practice for octogenarians. Second, only selected octogenarians who were judged able to withstand surgery were included in this study. However, more than half of the octogenarians in this study had an ASA physical status of two or three, and our results can be applied to the majority of older patients who are candidates for RC. Third, because the main focus of this study was

perioperative safety of LRC for older patients, the follow-up period was relatively short. Long-term observation is necessary for further evaluation of oncological outcomes. Fourth, this study was based on an LRC-only database, and comparison with open RC or other multidisciplinary approaches such as chemoradiation therapy was not performed. Despite these limitations, our multi-institutional study with a certain number of octogenarians represents significant real-world outcomes of these patients and proposes valuable information for decision-making.

In conclusion, LRC can be performed for selected octogenarians with complication rates similar to those of younger patients. Appropriate risk evaluation and modification of surgical procedures are necessary for older patients.

Acknowledgements The authors wish to acknowledge the assistance of the following individuals in this study: Kazuhiro Okumura, Hiroaki Kawanishi, and Yuka Kono from Tenriyorozu Hospital; Mutsushi Kawakita and Masashi Kubota from Kobe City Medical Center General Hospital; Noriyuki Ito and Yosuke Shimizu from Nishikobe Medical Center; Toshiyuki Kamoto and Masato Fujii from Miyazaki University; Tomomi Kamba and Kenichiro Tanoue from Kumamoto University; Yasumasa Shichiri and Akihiro Hamada from Otsu Municipal Hospital; Toshiya Akao and Noboru Shibasaki from Rakuwakai Otowa Hospital; Seiji Moroi and Go Kobori from Hamamatsu Rosai Hospital.

Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

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