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ORIGINAL SCIENTIFIC REPORT

Is Laparoscopic Gastrectomy More Advantageous for Elderly Patients Than for Young Patients with Resectable Advanced Gastric Cancer?

Yuki Ushimaru[1] · Yukinori Kurokawa[1] · Tsuyoshi Takahashi[1] · Takuro Saito[1] · Kotaro Yamashita[1] · Koji Tanaka[1] · Tomoki Makino[1] · Makoto Yamasaki[1] · Kiyokazu Nakajima[1] · Masaki Mori[2] · Yuichiro Doki[1]

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Abstract

Background Laparoscopic gastrectomy (LG) is now practiced widely, but it is unclear whether LG is the appropriate approach for elderly patients with resectable advanced gastric cancer. The aim of this study was to examine whether LG is more or less advantageous for elderly patients than for young patients.

Methods We collected data on 571 consecutive patients who underwent gastrectomy for pT2–4 gastric cancer between January 2001 and December 2015. After adjustment with one-to-one propensity score matching, short-term and long-term outcomes were compared between the LG and open gastrectomy (OG) groups among young (age < 70 years) and elderly (age ≥ 70 years) patients.

Results The LG group had a significantly longer operative time ($P < 0.001$) and less blood loss ($P < 0.001$) than the OG group among young and elderly patients. There were no significant differences regarding complications. Although disease-specific survival was similar between the LG and OG groups among young and elderly patients, LG was associated with more favorable overall survival than OG only among elderly patients (hazard ratio 0.67; 95% confidence interval 0.35–1.26). Death from respiratory diseases occurred more frequently in the OG group (10.9%) than in the LG group (0%) for elderly patients ($P = 0.012$).

Conclusion LG for resectable advanced gastric cancer was not inferior to OG in terms of both short-term and long-term outcomes regardless of patient age. In elderly patients, LG may improve overall survival by reducing mortality from respiratory diseases.

Introduction

Gastric cancer is the fifth most common malignancy in the world and the second leading cause of death among all malignancies worldwide [1]. Radical open gastrectomy (OG) is the curative treatment for gastric cancer [2]. Gastrectomy without complications leads to good long-term prognosis [3]. Over the last few decades, the aging population has affected healthcare provision, including surgical treatments [4, 5]. Aging has progressed most prominently in developed countries; in Japan, 21.4% of the population is aged 70 years or older [6]. Several studies have reported that aggressive surgical treatment has led to longer survival in elderly patients with gastric cancer [7–9]. As society ages, the number of surgical treatments for gastric cancer in elderly patients will increase.

Laparoscopic gastrectomy (LG) has been widely used in Japan since 1991 to treat gastric cancer [10]. The usefulness of LG has already been demonstrated for early gastric cancer with sufficient evidence [11–18]. Several

✉ Yukinori Kurokawa
ykurokawa@gesurg.med.osaka-u.ac.jp

[1] Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2-E2, Yamadaoka, Suita, Osaka 565-0871, Japan

[2] Department of Surgery and Science, Kyushu University Graduate School of Medicine, Fukuoka, Japan

randomized controlled trials (RCTs) comparing LG with OG for advanced gastric cancer are in progress, and its safety and feasibility have almost been established [19–21]. However, these trials excluded elderly patients from the eligibility criteria. Thus, the usefulness of LG for elderly patients remains unclear.

In our institution, we have been actively performing LG for gastric cancer since 2001. We have reported many surgical techniques and innovations [22–28]. Furthermore, we have also expanded the indications of LG for advanced gastric cancer without age limitations. Considering the recent rapidly aging community, it is necessary to evaluate the safety and efficacy of LG in elderly patients. We hypothesized that LG is more suitable than OG for elderly patients because it is less invasive. Thus, we conducted a propensity score matching (PSM) analysis to examine whether LG is more or less advantageous for elderly patients than for young patients with resectable advanced gastric cancer.

Patients and methods

Patients

We collected data on 571 consecutive patients who underwent gastrectomy for pT2–4 gastric cancer between January 2001 and December 2015 at Osaka University Hospital. Patients who underwent partial, R1, or R2 resection and patients who had remnant gastric cancer or atypical histology were ineligible. Patients who cannot tolerate general anesthesia due to severe comorbidities were excluded from the study. All patients were histologically diagnosed as having gastric adenocarcinoma. In general, patients underwent LG or OG with lymph node dissection according to the Japanese Gastric Cancer Treatment Guidelines [29]. LG was performed or supervised by surgeons who were certified by the Japan Society for Endoscopic Surgery according to the Endoscopic Surgical Skill Qualification System. Postoperative complications were evaluated based on the Clavien–Dindo classification [30]; we considered complications of grade II or higher to be postoperative complications in this study. TNM staging was determined on the basis of the 14th edition of the Japanese Classification of Gastric Carcinoma [31]. This study was approved by the Institutional Review Board of Osaka University Hospital (Approval number: 19201).

Statistical analysis

One-to-one PSM was used to reduce sampling bias and potential confounding factors by matching patients in the LG and OG groups. PSM analysis was conducted using a logistic regression model with the following covariates: age, sex, body mass index (BMI), American Society of Anesthesiologists physical status classification (ASA-PS), surgical procedure, histology, main tumor location, macroscopic type, tumor size, presence or absence of neoadjuvant chemotherapy, and pathological TNM stage. We used a caliper width of 0.2 for the pooled standard deviation of the logit for calculating the propensity score. After PSM, we divided the patients into two populations: elderly patients, consisting of patients aged 70 years or more, and young patients under 70 years.

Overall survival (OS) was defined as the period from the date of surgery to the date of death from any cause. Disease-specific survival (DSS) was defined as the period from the date of surgery to the date of death due to primary disease. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. We compared the clinicopathological characteristics of the LG and OG groups using the Chi-squared test for categorical variables and the Mann–Whitney U test for continuous variables. $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using JMP® PRO software (JMP version 14.1.0, SAS Institute, Cary, NC).

Results

Patient characteristics

The study flowchart is summarized in Fig. 1. After 188 patients in the LG group and 383 patients in the OG group underwent PSM, 137 pairs of patients were analyzed. Of 274 patients, 172 patients (62.8%) were young (age $<$ 70 years) patients and 102 (37.2%) were elderly (age $\geq$ 70

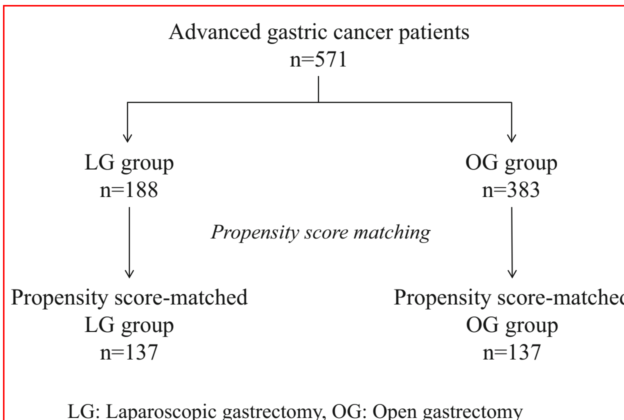

Fig. 1 Study flowchart

years) patients. Total gastrectomy was performed for 44.2% of young patients and 30.4% of elderly patients. The proportions of pathological stage I, II, and III disease were 19.2%, 49.4%, and 31.4%, respectively, for young patients and 15.7%, 52.9%, and 31.4%, respectively, for elderly patients. Adjuvant chemotherapy was performed in 53.5% of young patients and 32.4% of elderly patients. The differences in clinicopathological characteristics between the LG and OG groups are summarized in Table 1. No significant differences were observed between the two groups in any factors between young and elderly patients.

Short-term outcomes

Comparisons of short-term outcomes between the young and elderly patients are summarized in Table 2. The LG group had a significantly longer operative time ($P < 0.001$) and less blood loss ($P < 0.001$) than the OG group among both young and elderly patients. The number of retrieved lymph nodes did not differ significantly between the LG and OG groups among young ($P = 0.19$) and elderly patients ($P = 0.43$).

Regarding surgical complications, the overall incidence of Clavien–Dindo grade II–IV surgical complications did not differ significantly among young (LG, 16.1%; OG, 22.0%; $P = 0.32$) and elderly patients (LG, 19.6%; OG, 30.4%; $P = 0.21$). There was no significant difference for each complication between the LG and OG groups among young and elderly patients. No in-hospital mortality or 30-day mortality occurred in either group.

Long-term outcomes

At the median follow-up duration of 63.2 months for all censored patients, we estimated DSS and OS. In the DSS analysis (Fig. 2), the LG and OG groups had similar survival curves among young (hazard ratio [HR] 1.02; 95% confidence interval [CI] 0.52–2.02; log-rank $P = 0.95$) and elderly patients (HR 1.00; 95% CI 0.41–2.42; log-rank $P = 1.00$). In the OS analysis (Fig. 3), LG showed a non-significant difference, but a trend toward improved survival compared with OG (HR 0.67; 95% CI 0.35–1.26; log-rank $P = 0.21$) among elderly patients, although the LG and OG groups had similar survival curves among young patients (HR 0.88; 95% CI 0.47–1.67; log-rank $P = 0.70$).

Regarding the cause of death, the proportions of death from primary cancer were very similar between the LG and OG groups among young (LG 19.8%; OG18.6%; $P = 0.86$) and elderly patients (LG 19.6%; OG 19.6%; $P = 0.99$) (Table 3). On the other hand, elderly patients in the OG group had a nonsignificant difference but a trend toward a higher proportion of death from other diseases (LG 10.7%; OG 28.3%; $P = 0.14$). In particular, death from respiratory diseases occurred more frequently in the OG group than in the LG group among elderly patients (LG 0%; OG 10.9%; $P = 0.012$), although no young patients died due to respiratory diseases in either group. A total of nine patients died of secondary cancers diagnosed during the postoperative follow-up period.

Discussion

In this PSM study, we confirmed LG required significantly longer operative time, but there was less blood loss than OG among both young and elderly patients. In addition, there were no statistically significant differences regarding complications. Among long-term outcomes, DSS was quite similar between the LG and OG groups among both young and elderly patients. However, LG was associated with more favorable OS than OG among elderly patients only. This is probably because elderly patients who underwent LG were less likely to die from other diseases, such as respiratory diseases, than elderly patients who underwent OG.

Many studies have demonstrated the benefits of LG, which include improved cosmetic effect, less pain, quicker recovery, shorter hospital stay, and better quality of life [13, 32–35]. Recent retrospective studies have also suggested the non-inferiority of LG compared with OG in terms of long-term outcomes [36–38]. Three large-scale RCTs comparing LG and OG have been conducted for advanced gastric cancer; short-term outcomes have already been reported to be satisfactory in these studies [19–21]. For long-term prognosis, one of the three studies recently showed the non-inferiority of LG [39], although two of the three studies are still ongoing. Of these three RCTs, inclusion criteria included age up to 80 years for two studies and up to 75 years for one study. Thus, many elderly patients with gastric cancer were excluded from these studies. There have been few studies comparing LG and OG in patients with advanced gastric cancer after stratification for age. In this study, we examined how LG and OG affect prognosis after stratification into young and elderly patients with advanced gastric cancer.

Elderly patients often have more comorbidities such as hypertension and diabetes than young patients [40]. We reported that elderly patients have significantly lower preoperative serum albumin levels and higher ASA-PS scores than young patients [41]. These high-risk conditions are probably responsible for some nonsurgical complications after gastrectomy in elderly patients. Gastrectomy for the elderly is associated with a higher incidence of postoperative pneumonia, which is directly linked to mortality [42, 43]. We also reported that a low preoperative prognostic nutrition index and multiple comorbidities are

Table 1 Patient characteristics

	Young patients			Elderly patients		
	LG group (*n* = 81)	OG group (*n* = 91)	*P* value	LG group (*n* = 56)	OG group (*n* = 46)	*P* value
Age (years)*	61 (31–69)	61 (35–69)	0.73	77 (70–89)	76 (70–89)	0.91
Sex						
Male	57 (70.4%)	67 (73.6%)	0.63	43 (76.8%)	34 (73.9%)	0.74
Female	24 (29.6%)	24 (26.4%)		13 (23.2%)	12 (26.1%)	
ASA-PS						
1	32 (39.5%)	38 (41.8%)	0.73	15 (26.8%)	11 (23.9%)	0.94
2	44 (54.3%)	45 (49.5%)		29 (51.8%)	25 (54.3%)	
3	5 (6.2%)	8 (8.8%)		12 (21.4%)	10 (21.7%)	
Body mass index (kg/m^2)*	21.9 (13.9–31.9)	22.0 (15.1–31.0)	0.82	21.5 (13.3–32.5)	21.0 (16.9–33.1)	0.34
Main tumor location						
Upper	31 (38.3%)	36 (39.6%)	0.72	17 (30.4%)	11 (23.9%)	0.74
Middle	29 (35.8%)	36 (39.6%)		20 (35.7%)	19 (41.3%)	
Lower	21 (25.9%)	19 (20.9%)		19 (33.9%)	16 (34.8%)	
Macroscopic type						
0, 1, 2	43 (53.1%)	45 (49.5%)	0.63	35 (62.5%)	29 (63.0%)	0.95
3, 4, 5	38 (46.9%)	46 (50.5%)		21 (37.5%)	17 (37.0%)	
Tumor size (mm)*	42 (12–130)	49 (12–135)	0.21	40 (18–160)	40 (16–100)	0.68
Histological type						
Differentiated	36 (44.4%)	37 (40.7%)	0.61	32 (57.1%)	26 (56.5%)	0.95
Undifferentiated	45 (55.6%)	54 (59.3%)		24 (42.9%)	20 (43.5%)	
Type of gastrectomy						
Total	34 (42.0%)	42 (46.2%)	0.36	17 (30.4%)	14 (30.4%)	0.80
Proximal	8 (9.9%)	4 (4.4%)		3 (5.4%)	4 (8.7%)	
Distal	39 (48.1%)	45 (49.5%)		36 (64.3%)	28 (60.9%)	
Lymphadenectomy						
<D2	12 (14.8%)	11 (12.1%)	0.60	17 (30.4%)	13 (28.3%)	0.82
≥D2	69 (85.2%)	80 (87.9%)		39 (69.6%)	33 (71.7%)	
pT status						
T2	28 (34.6%)	23 (25.3%)	0.26	22 (39.3%)	20 (43.5%)	0.16
T3	40 (49.4%)	46 (50.5%)		14 (25.0%)	17 (37.0%)	
T4	13 (16.0%)	22 (24.2%)		20 (35.7%)	9 (19.6%)	
pN status						
N0	34 (42.0%)	45 (49.5%)	0.76	19 (33.9%)	22 (47.8%)	0.54
N1	22 (27.2%)	22 (24.2%)		15 (26.8%)	10 (21.7%)	
N2	12 (14.8%)	13 (14.3%)		13 (23.2%)	9 (19.6%)	
N3	13 (16.0%)	11 (12.1%)		9 (16.1%)	5 (10.9%)	
Pathological stage						
I	17 (21.0%)	16 (17.6%)	0.79	5 (8.9%)	11 (23.9%)	0.11
II	38 (46.9%)	47 (51.6%)		31 (55.4%)	23 (50.0%)	
III	26 (32.1%)	28 (30.8%)		20 (35.7%)	12 (26.1%)	
Neoadjuvant chemotherapy						
Present	14 (17.3%)	19 (20.9%)	0.55	4 (7.1%)	4 (8.7%)	0.77
Absent	67 (82.7%)	72 (79.1%)		52 (92.9%)	42 (91.3%)	

Table 1 continued

	Young patients LG group (n = 81)	OG group (n = 91)	P value	Elderly patients LG group (n = 56)	OG group (n = 46)	P value
Adjuvant chemotherapy						
Present	48 (59.3%)	44 (48.4%)	0.15	21 (37.5%)	12 (26.1%)	0.22
Absent	33 (40.7%)	47 (51.6%)		35 (62.5%)	34 (73.9%)	

ASA-PS American Society of Anesthesiologists physical status classification

*Median (range)

Table 2 Short-term outcomes

	Young patients			Elderly patients		
	LG group (n = 81)	OG group (n = 91)	P value	LG group (n = 56)	OG group (n = 46)	P value
Operation time (min)*	249 (117–635)	220 (105–520)	< 0.001	262 (136–511)	204 (99–745)	< 0.001
Intraoperative blood loss (ml)*	100 (10–2100)	480 (20–4800)	< 0.001	100 (20–1550)	450 (20–3750)	< 0.001
Number of retrieved lymph nodes*	39 (14–89)	37 (13–131)	0.19	30 (14–72)	31 (13–60)	0.43
Overall surgical complications (≥ Clavien–Dindo grade II)	13 (16.1%)	20 (22.0%)	0.32	11 (19.6%)	14 (30.4%)	0.21
Surgical site infection	3 (3.7%)	4 (4.4%)	0.82	2 (3.6%)	4 (8.7%)	0.27
Pancreatic fistula	4 (4.9%)	3 (3.3%)	0.59	2 (3.6%)	2 (4.4%)	0.84
Anastomotic leakage	3 (3.7%)	3 (3.3%)	0.88	1 (1.8%)	1 (2.2%)	0.89
Respiratory disease	0 (0.0%)	1 (1.1%)	0.26	2 (3.6%)	5 (10.9%)	0.14
Intra-abdominal bleeding	1 (1.2%)	1 (1.1%)	0.93	0 (0.0%)	1 (2.2%)	0.21
Anastomotic bleeding	1 (2.6%)	0 (0.0%)	0.27	2 (3.6%)	0 (0.0%)	0.12
Others	1 (1.2%)	6 (6.6%)	0.06	3 (5.4%)	2 (4.4%)	0.81
Reoperation	0 (0.0%)	2 (2.2%)	0.11	1 (1.8%)	0 (0.0%)	0.27
Postoperative mortality (< 30 days)	0 (0.0%)	0 (0.0%)	–	0 (0.0%)	0 (0.0%)	–

*Median (range)

significant risk factors for death from other diseases within 5 years in elderly patients [44]. Kiuchi et al. [45] reported that postoperative pneumonia is less common after LG (0.9%) versus OG (2.6%). Indeed, there was the possibility that patients with severe respiratory or cardiac comorbidities tended to receive OG. However, as laparoscopic surgery has the advantage of causing less abdominal wall injury, LG may lead to fewer postoperative respiratory complications in elderly patients. This advantage of LG could lead to lower mortality from respiratory diseases during long-term follow-up as well.

There are several limitations in this study. First, this study is a retrospective study and includes several sources of selection bias. In order to reduce these biases, PSM was performed. Background factors were well balanced after PSM. In general, OG tends to be selected for more advanced cases, but our selection process usually depends on ongoing clinical trials rather than tumor status. Second, there is still no consensus on the age cutoff between young and elderly patients. Frailty is especially important in cancer treatment [46]. We used 70 years as the age cutoff in this study because it is usually recommended that all elderly patients aged over 70 years be routinely assessed for frailty [47]. It may be necessary to examine to use a higher age cutoff in the near future, considering the speed of aging in society. Third, due to the long study period, the historical background is somewhat different. For example, the ACTS-GC trial demonstrated the survival benefit of postoperative S-1 in 2007 [48]. Later, adjuvant S-1 chemotherapy was determined to be the standard treatment for pStage II–III gastric cancer. Thus, the change in standard treatment over time may have influenced differences in prognosis for LG versus OG.

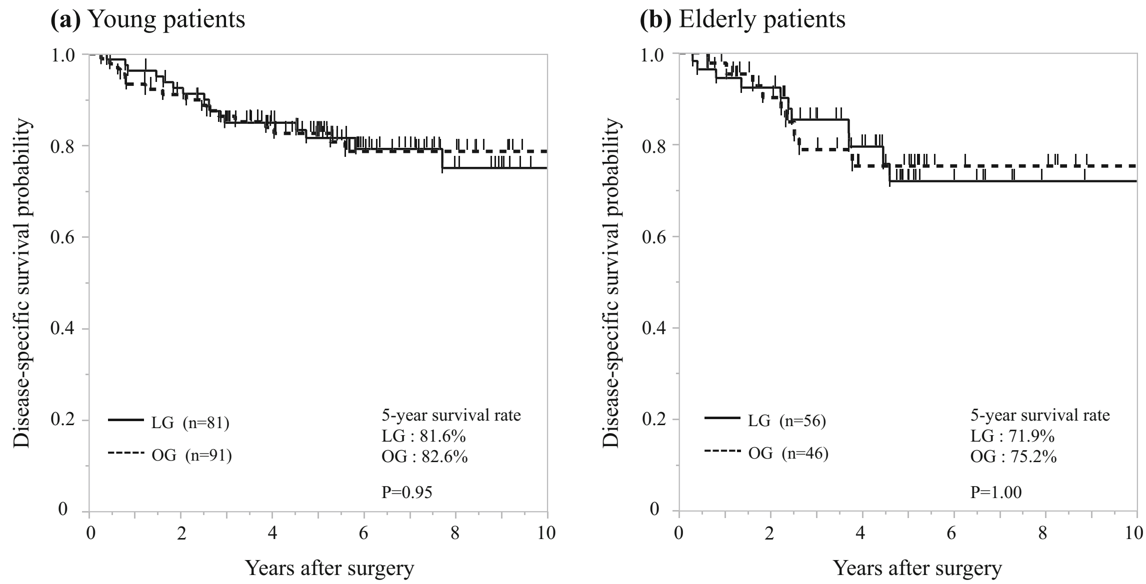

Fig. 2 Disease-specific survival curves of the laparoscopic gastrectomy (LG) and open gastrectomy (OG) groups for young patients (< 70 years) (**a**) and elderly patients (≥ 70 years) (**b**)

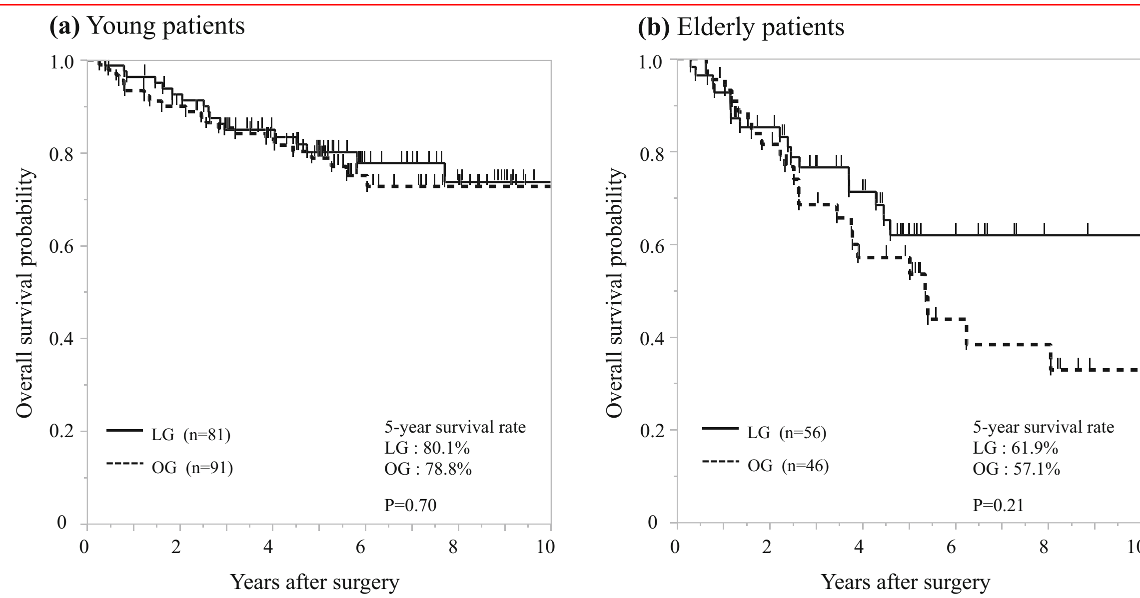

Fig. 3 Overall survival curves of the laparoscopic gastrectomy (LG) and open gastrectomy (OG) groups for young patients (< 70 years) (**a**) and elderly patients (≥ 70 years) (**b**)

In conclusion, LG for resectable advanced gastric cancer is not inferior to OG in terms of short-term and long-term outcomes. However, in elderly patients, LG may improve OS by reducing mortality from other diseases due to its lower invasiveness. Thus, the advantage of LG would be higher for elderly patients than for young patients with advanced gastric cancer. If the ongoing RCTs demonstrate the non-inferiority of LG versus OG for relatively young patients with advanced gastric cancer, the results can be generalized to elderly patients.

Table 3 Causes of death

	Young patients			Elderly patients		
	LG group (*n* = 81)	OG group (*n* = 91)	*P* value	LG group (*n* = 56)	OG group (*n* = 46)	*P* value
Death from primary cancer	16 (19.8%)	17 (18.6%)	0.86	11 (19.6%)	9 (19.6%)	0.99
Death from other diseases	1 (1.2%)	4 (4.4%)	0.22	6 (10.7%)	13 (28.3%)	0.14
Other cancer deaths	1 (1.2%)	2 (2.2%)	0.68	3 (5.4%)	3 (6.5%)	0.73
Respiratory disease	0 (0%)	0 (0%)	–	0 (0%)	5 (10.9%)	0.012
Heart failure	0 (0%)	2 (2.2%)	0.12	2 (3.6%)	1 (2.2%)	0.40
Senile decay	0 (0%)	0 (0%)	–	1 (2.2%)	2 (4.3%)	0.71
Liver failure	0 (0%)	0 (0%)	–	0 (0%)	1 (2.2%)	0.28
Sepsis	0 (0%)	0 (0%)	–	0 (0%)	1 (2.2%)	0.28

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Compliance with ethical standards

Conflict of interest There is no conflict of interest regarding the manuscript.

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