Title

Chemotherapy in cancer patients undergoing haemodialysis: a nationwide study in Japan

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Abstracts

Background: Cancer is a major cause of death in patients undergoing haemodialysis. However, information about the actual clinical practice of chemotherapy for patients with cancer undergoing haemodialysis is lacking. We conducted a nationwide survey using questionnaires on the clinical practice of chemotherapy for such patients.

Patients and methods: The nationwide survey included patients undergoing haemodialysis who were subsequently diagnosed with cancer in 20 hospitals in Japan from January 2010 to December 2012. We reviewed their clinical data, including cancer at the following primary sites: kidney, colorectum, stomach, lung, liver, bladder, pancreas, and breast. The questionnaires consisted of the following subjects: (1) patient characteristics; (2) regimen, dosage, and timing of chemotherapy; and (3) clinical outcome.

Results: Overall, 675 patients were registered and assessed for main primary cancer site involvement. Of 507 patients with primary site involvement, 74 patients (15%) received chemotherapy (44 as palliative chemotherapy and 30 as perioperative chemotherapy). The most commonly used cytotoxic drugs were fluoropyrimidine (15 patients), platinum (eight patients), and taxane (eight patients), and the dosage and timing of these drugs differed between institutions; however, the dosage of molecular targeted drugs (24 patients) and hormone therapy drugs (15 patients) was consistent. The median survival time of patients receiving palliative chemotherapy was 13.0 months (0.1–60.3 months). Three patients (6.8%) died from treatment-related causes and nine patients (20%) died of causes other than cancer. Of the 30 patients who received perioperative chemotherapy, six (20%) died of causes other than cancer within 3 years after the initiation of chemotherapy.

Conclusion: Among the haemodialysis patients with cancer who received chemotherapy, the rates of mortality from causes other than cancer might be high for both palliative and perioperative chemotherapy. Indications for the use of chemotherapy in patients undergoing haemodialysis should be considered carefully.

Key questions

What is already known about this subject?

- Cancer is one of the major causes of death among haemodialysis patients.
- There are no guidelines regarding chemotherapy for haemodialysis cancer patients.
- Few data are available about the actual clinical practice of chemotherapy for haemodialysis cancer patients.

What does this study add?

- Our results showed details of the treatment and clinical outcomes of haemodialysis patients who received cancer chemotherapy.
- The non-cancer-related mortality is high in haemodialysis patients who receive chemotherapy.
- The dosage and timing of cytotoxic drugs such as 5-fluorouracil and platinum differed between institutions.

How might this impact on clinical practice?

- The indications of chemotherapy for cancer patients undergoing haemodialysis should be carefully considered.
- The optimal timing and necessary dose adjustments of anticancer drugs in the context of dialysis sessions should be investigated.

Introduction

Currently, the number of dialysis patients has increased worldwide. The dialysis population is over two million worldwide and 300,000 in Japan [1, 2]. The risk of cancers such as kidney and bladder cancer in patients undergoing haemodialysis (HD) is generally higher than in the general population [3], and cancer is one of the major causes of death among HD patients, ranking third in Japan after cardiac failure and infectious disease [2, 4].

Chemotherapy is a standard treatment for advanced cancers in a palliative and perioperative setting. Several randomized trials testing new treatments for various advanced cancers have shown a survival benefit. However, the subjects of these clinical trials are limited to patients with adequate organ function. There has been no clinical trial which verifies the efficacy and safety of chemotherapy in the HD patient.

As the number of HD patients increases, medical oncologists and nephrologists are more likely to treat cancer patients undergoing HD and to confront the difficulty of managing their chemotherapy [5, 6]. However, there are no guidelines regarding cancer chemotherapy for HD patients due to a lack of evidence [7]. Furthermore, few data are available about the actual clinical practice of managing chemotherapy in HD patients. Only one study, the CANDY study conducted in France, has reported the clinical practice of chemotherapy in cancer patients undergoing HD [8]. The CANDY study focused on the type of anticancer drugs used and dose adjustment for patients undergoing HD. However, the clinical outcomes, such as efficacy and adverse events, were not discussed; therefore, physicians still face challenges in providing cancer chemotherapy. A lack of knowledge and data concerning the use of chemotherapy may lead to improper use of chemotherapy and fatal toxic effects in patients undergoing HD.

We conducted a nationwide survey of cancer patients undergoing HD and receiving chemotherapy. We reviewed the clinical outcome in addition to the regimen and dosage of chemotherapy.

Patients and methods

This retrospective case series study was conducted by the Onco-Nephrology Consortium in Japan with clinical investigators, both medical oncologists and nephrologists, from 20 institutions. We enrolled patients undergoing HD who were subsequently diagnosed with cancer in the participating institutes from January 2010 to December 2012. We reviewed the clinical courses of those patients who met the following selection criteria: 1) primary sites of the cancer were in the kidney, colorectum, stomach, lung, bladder, liver, breast, or pancreas; 2) the initial treatments were palliative chemotherapy or surgery followed by perioperative chemotherapy. We selected the eight primary sites because they were represented at a high frequency in our preliminary survey. We excluded patients with a history of renal transplantation. This study was approved by the institutional review board or ethics committee at each participating institution.

Data collection

In July 2014, the same questionnaires were sent by e-mail to members of the Onconephrology Consortium of 20 institutions in Japan. Twelve of these were general hospitals and eight were university hospitals. The questionnaires consisted of the following sections: (1) patient characteristics (age, sex, primary disease of renal failure, duration of HD, symptoms due to cancer, disease status, and Eastern Cooperative Oncology Group performance status); (2) regimen, dosing, and timing of chemotherapy; and (3) clinical outcome (response rate, adverse events, survival time, and cause of death). The data were collected from medical records until the point of the most recent follow-up. The deadline for submission was November 2015.

Response and toxicity evaluation

Objective response was assessed according to the Response Evaluation Criteria in Solid Tumors (version 1.1). The toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Treatment-related death was defined as any cause of death which occurred within 30 days after the initiation of chemotherapy.

Statistical analysis

Overall survival was calculated from the initiation of treatment to the date of death from any cause. Survival curves were calculated by the Kaplan–Meier method using IBM statistics software (version 21.0; IBM, Armonk, NY, USA).

Results

Subjects

Overall, 675 patients with cancer undergoing HD were registered in this study. The primary cancer sites were, kidney (161 patients), colorectum (84 patients), stomach (73 patients), lung (64 patients), bladder (37 patients), liver (35 patients), breast (27 patients), and pancreas (26 patients). Among these patients, 396 cancers were assessed to be surgically resectable, 107 were assessed to be unresectable, and the disease status of the remaining four patients was unknown. Of the 107 patients with unresectable cancer, 44 underwent chemotherapy, 36 received best supportive care, and 27 patients underwent other therapies. The reasons for best supportive care were older age (14 patients), poor performance status (11 patients), no indication for chemotherapy (nine patients), critical comorbidities such as severe heart disease and cerebral infarction (eight patients), patient/family decision (seven patients), and unknown (five patients) (13 patients overlapped). Finally, 74 patients met the selection criteria and received chemotherapy as the initial treatment (44 as palliative chemotherapy and 30 as perioperative chemotherapy). The consort diagram is shown in Supplementary Figure 1. The baseline characteristics of the 74 patients are shown in Table 1. The median age of patients and duration of HD were 64 (range, 44–81) and 8.8 (range, 0.3–37.2) years, respectively, in the palliative group and 68 (range, 43–85) and 9.2 (range, 0.1–27.7) years, respectively, in the perioperative group. The primary causes of renal failure were chronic glomerulonephritis and diabetic nephropathy in both groups. The primary cancer sites were kidney (18 patients), lung (nine patients), colorectum (seven patients) in the palliative group, and breast (17 patients) and colorectum (six patients) in the perioperative group.

Anticancer drugs prescribed in this study

The anticancer drugs prescribed in this study were cytotoxic drugs in 34 patients, molecular targeted drugs in 24 patients, hormone therapy drugs in 15 patients, and other drugs in four patients (Table 2). The cytotoxic drugs used most commonly were fluoropyrimidine (15 patients), platinum (eight patients), and taxane (eight patients). Most of the molecular targeted drugs were used for renal cell cancer (17 patients) and all hormone therapy drugs were used for breast cancer. Regarding the dosage and timing of chemotherapy, the 5-fluorouracil dose was reduced by 20-30% in three patients in consideration of renal dysfunction. Most of the taxanes, gemcitabine, and monoclonal antibodies were administered on non-dialysis days. Notably, the dosage and timing of platinum differed among institutions. In eight patients who received platinum containing chemotherapy at eight different institutions, the timing of platinum administration was just before the HD session on a dialysis day in four patients and on a nondialysis day in four patients. The dosage of oxaliplatin was reduced by 30% in two patients and the dosage of cisplatin was reduced by 50% in one patient.

However, the dosage of molecular targeted drugs (24 patients) and hormone therapy drugs (15 patients) was consistent among participating institutions; most of the hormone therapy drugs and molecular targeted drugs were used without dose adjustment (Table 2). The dosage of sorafenib was reduced by 50% (400 mg/day) in all patients and the dosage of sunitinib was reduced by 25-50% (37.5mg/day or 25mg/day) in four patients.

Response, clinical course, and adverse events

Of the 22 patients with measurable lesions in the palliative group, five patients achieved partial response and eight patients were stable. The adverse events, grade 3 or higher, of cytotoxic and molecular drugs are listed in Table 3. Among the 10 patients who received perioperative cytotoxic chemotherapy, five patients completed the planned regimen. Three patients who received tegafur/uracil at an adjusted dosage completed the planned regimen without experiencing G3 or higher adverse events. Three patients, who received 5-FU or gemcitabine at the standard dose, discontinued adjuvant chemotherapy due to severe adverse events including grade 4 sepsis, grade 3

pneumonitis, and grade 3 small intestinal mucositis. Among 10 patients who received molecular targeted drug monotherapy at the standard dose in the palliative group, eight patients could continue chemotherapy at the initial dosage without severe adverse events. One patient who received erlotinib required a dose adjustment due to diarrhea and one patient who received everolimus discontinued chemotherapy due to grade 3 pneumonitis. As for pneumonitis, three patients—receiving gemcitabine at an 80% dosage, sorafenib at a 50% dosage, or everolimus at the standard dosage—experienced G3 or higher pneumonitis within 2 months of the initiation of chemotherapy. All three patients improved with the discontinuation of chemotherapy and steroid therapy, yet they were unable to receive subsequent chemotherapy.

Severe adverse events leading to hospitalization or death were reported in 15 patients including three treatment-related deaths: sudden death in two patients and sepsis in one patient. However, there were no severe adverse events in the hormone therapy group.

Survival and cause of death

After a median follow-up time of 14.1 months (0.1–52.2 months), the median survival time of 44 patients who received palliative chemotherapy was 13.0 months (Figure 1). Regarding the cause of deaths, 19 patients (68%) died of cancer and nine patients (32%) died of causes other than cancer (Figure 2). Among five patients whose primary cause of renal failure was diabetic nephropathy, three patients (60%) died of causes other than cancer, including two treatment-related deaths (infection, sudden death). Of 30 patients who received perioperative chemotherapy, the 3-year survival rate was 79% after a median follow-up time of 31.5 months (11.7–60.9 months). Regarding the cause of deaths, one patient (14%) died of cancer and six patients (86%) died of causes other than cancer within 3 years after chemotherapy was initiated. All non-cancer-related causes of death occurred after chemotherapy had ended; therefore, they were considered unrelated to chemotherapy.

Discussion

This is the largest case series study of chemotherapy in cancer patients undergoing HD. It will enable us to recognize what we should consider when managing chemotherapy for these patients in clinical

practice.

The prognosis of dialyzed patients is poor compared with nondialyzed patients because dialyzed patients are compromised and have several complications. According to the results of a Japanese nationwide survey, the annual death rate of dialyzed patients has remained in the range 9.2–10.2% since 1992, whereas since 1995, that of the general Japanese population aged 60–64 years, 70–74 years, and 80–84 years has remained in the range 0.6–0.9%, 1.5–2.2%, and 4.4–6.9%, respectively [2, 9]. This poor prognosis of dialyzed patients mainly due to cardiac failure and infectious disease may have influenced the high non-cancer-related death rate in this study.

Generally, the main purpose of perioperative chemotherapy is to reduce cancer recurrence and to prolong survival. Therefore, perioperative chemotherapy is indicated for patients who are expected to survive for extended periods after their cancer is cured. For example, the non-cancer-related 5-year mortality rate of breast cancer patients who were treated with surgery followed by adjuvant tamoxifen was 3.7% [10]. Similarly, the non-cancer-related 6-year mortality rate of colorectal cancer patients who were treated with surgery followed by adjuvant FOLFOX4 therapy was 5.8% [11]. However, in this study, six patients (20%) died of causes other than cancer within 3 years after the initiation of perioperative chemotherapy. Compared with the results for nondialyzed patients, the non-cancer-related mortality rate in HD patients was clearly higher. This suggests that the prognosis should be taken into account when considering the indications for perioperative chemotherapy in patients undergoing HD.

In the palliative chemotherapy group (n = 44), the rate of treatment-related death was 6.8%. One cause of treatment-related death was infection. A 76-year-old man with a wild-type UGT1A1 allele received irinotecan at a dosage of 150 mg/m^2 as part of FORFIRI plus cetuximab chemotherapy. This patient died of sepsis with grade 4 neutropenia within 1 month of treatment. Fujita et al. previously reported that in patients with severe renal failure, the area under the concentration–time curve for SN-38, the active metabolite of irinotecan, was much greater than that of patients with normal kidney function, although neither irinotecan nor SN-38 is excreted by the kidneys [12]. This might be the cause of the severe neutropenia and infection in this patient. Because

patients undergoing HD are potentially compromised, we should carefully decide the regimen and dosage of chemotherapy to avoid fecal infection.

The other problem is that the dosage and timing of cytotoxic drugs such as fluoropyrimidine and platinum differed between institutions in this study. This different administration of chemotherapy is due to the paucity of pharmacokinetic data. For example, there is a lack of data available about whether platinum can be dialyzed. Several case reports have recommended that a dialysis session is initiated immediately after the administration of oxaliplatin to remove circulating platinum molecules derived from oxaliplatin, which have biological activity [13–15]. However, most circulating platinum molecules are undialyzable because they are immediately bound to plasma proteins or distributed to the tissue. Therefore, the adequate dosage and timing of platinum administration are unclear. However, by referring to data from the literature with sufficient pharmacokinetic data, the dosage of sorafenib in this study was consistently reduced [16]. Pharmacokinetic study is needed to establish the optimal chemotherapy for cancer patients undergoing HD. Therefore, we conducted a pharmacokinetic study of 5-fluorouracil and oxaliplatin, both of which were commonly used in this study, in cancer patients undergoing HD [17].

This study has some limitations. First, this study is retrospective; therefore, the possibility of bias exists in the selection of patients. In this study, we collected the data only from the patients undergoing HD with cancer who were treated in a cancer hospital because we could not collect the data of those who could not be treated for reasons such as patient refusal or their medical condition. Therefore, this might affect the evaluation of efficacy and safety of chemotherapy for the cancer patients undergoing HD. Second, the subjects in this study included various cancers and chemotherapy regimens. Although the incidence of grade 3 or higher adverse events was relatively low, it might be due to reduced dosage of anticancer drugs and underestimated by retrospective analysis. Therefore, it is rather difficult to evaluate the efficacy and adverse events of a given chemotherapy regimen. Third, the follow-up period to evaluate the survival data is short. However, the problem of poor outcome and the method of anticancer drugs administration can be discussed. Furthermore, 12 (27%) of 44 unresectable cancer patients lived more than two years in this study,

effective chemotherapy may provide a chance of long survival even for HD patients with unresectable cancer. In the current situation where there is a lack of information, our present data may facilitate clinical decision making and future advancements in cancer chemotherapy for patients undergoing HD.

In conclusion, among the patients with cancer who were undergoing HD and received chemotherapy, the rates of mortality from causes other than cancer might be high for both palliative and perioperative chemotherapy. The prognosis of dialyzed patients is poor compared with that of nondialyzed patients. Therefore, the indications of chemotherapy for patients undergoing HD should be carefully considered.

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References

1. Liyanage T, Ninomiya T, Jha V et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet 2015; 385: 1975–1982.
2. Masakane I, Nakai S, Ogata S et al. An overview of regular dialysis treatment in Japan (as of 31 December 2013). Ther Apher Dial 2015; 19: 540–574.
3. Maisonneuve P, Agodoa L, Gellert R et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 1999; 354: 93–99.
4. de Jager DJ, Grootendorst DC, Jager KJ et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. JAMA 2009; 302: 1782–1789.
5. Kitai Y, Matsubara T, Yanagita M. Onco-nephrology: current concepts and future perspectives. Jpn J Clin Oncol 2015; 45: 617–628.
6. Kitai Y, Matsubara T, Funakoshi T et al. Cancer screening and treatment in patients with end-stage renal disease: remaining issues in the field of onco-nephrology. Renal Replacement Therapy 2016;

2: 1–9.

7. Janus N, Thariat J, Boulanger H et al. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. Ann Oncol 2010; 21: 1395–1403.

8. Janus N, Launay-Vacher V, Thyss A et al. Management of anticancer treatment in patients under chronic dialysis: results of the multicentric CANDY (CANcer and DialYsis) study. Ann Oncol 2013; 24: 501–507.

9. Vital Statistics of Japan. Tokyo, Japan: Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare, 1995-2015.

10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011; 27: 771–784.

11. Andre T, Boni C, Navarro M et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009; 27: 3109–3116.

12. Fujita K, Masuo Y, Okumura H et al. Increased plasma concentrations of unbound SN-38, the active metabolite of irinotecan, in cancer patients with severe renal failure. Pharm Res 2016; 33: 269–282.

13. Watayo Y, Kuramochi H, Hayashi K et al. Drug monitoring during FOLFOX6 therapy in a rectal cancer patient on chronic hemodialysis. Jpn J Clin Oncol 2010; 40: 360–364.

14. Horimatsu T, Miyamoto S, Morita S et al. Pharmacokinetics of oxaliplatin in a hemodialytic patient treated with modified FOLFOX-6 plus bevacizumab therapy. Cancer Chemother Pharmacol 2011; 68: 263–266.

15. Gori S, Lunardi G, Inno A et al. Pharmacokinetics of oxaliplatin in a hemodialyzed patient: chemotherapy dose adjustment and timing of dialysis. Clin Colorectal Cancer 2014; 13: 260–263.

16. Kennoki T, Kondo T, Kimata N et al. Clinical results and pharmacokinetics of sorafenib in chronic hemodialysis patients with metastatic renal cell carcinoma in a single center. Jpn J Clin Oncol 2011; 41: 647–655.

17. Funakoshi T, Horimatsu T, Yamada A et al. Pharmacokinetics and safety of FOLFOX therapy in

patients undergoing hemodialysis. Ann Oncol 2017; 28 (suppl_5): v543-v567.

Table 1. Patients' characteristics

	Palliative group *N* = 44	Perioperative group *N* = 30
Median age, year (range)	64 (44–81)	68 (43–85)
Sex		
Male	36 (82%)	10 (33%)
Female	8 (18%)	20 (67%)
Primary causes of renal failure		
Chronic glomerulonephritis	15 (34%)	8 (27%)
Diabetic nephropathy	11 (25%)	6 (20%)
Nephrosclerosis	6 (14%)	1 (3%)
Others	12 (27%)	15 (50%)
Median duration of haemodialysis, year (range)	8.8 (0.3–37.2)	9.2 (0.1–27.7)
Primary site		
Kidney	18	0
Lung	9	0
Colorectum	7	6
Stomach	4	1
Pancreas	3	3
Breast	2	17
Bladder	1	3
Symptoms due to cancer		
Yes	21 (48%)	18 (60%)
No	23 (52%)	12 (40%)
Disease status		
Resectable disease		30 (100%)
Locally advanced disease	6 (14%)	
Metastatic disease	38 (86%)	
ECOG performance status		
0 to 1	27 (61%)	18 (60%)
≥2	8 (18%)	1 (3%)
Unknown	9 (21%)	11 (37%)

Table 2. Anticancer drugs prescribed in this study

	N	Dosage adjustment	
		No	Yes
［Cytotoxic drugs］			
Fluoropyrimidine			
5-fluorouracil	9	67%	33%
Tegafur/uracil	6	17%	67%
Platinum			
Oxaliplatin	4	50%	50%
Carboplatin	2	50%	50%
Cisplatin	2	50%	50%
Taxane			
Paclitaxel	4	25%	75%
Docetaxel	4	-	100%
Others			
Gemcitabine	7	57%	43%
Irinotecan	3	33%	67%
Other drugs	4	-	-
［Molecular targeted drugs］			
Sorafenib	6	-	100%
Sunitinib	4	-	100%
Temsirolimus	4	100%	-
Everolimus	2	50%	50%
Erlotinib	2	100%	-
Trastuzumab	2	100%	-
Cetuximab	1	100%	-
Panitumumab	1	100%	-
Imatinib	1	100%	-
Axitinib	1	100%	-
［Hormonal therapy drugs］			
Aromatase inhibitor	11	100%	-
LH-RH agonist	2	100%	-
Tamoxifen	2	100%	-

The status of tegafur/uracil dosage adjustment is unknown in one patient.

Table 3. Adverse events of grade 3 or higher

	Cytotoxic drugs only ($N = 31$)	Molecular targeted drugs only ($N = 21$)	Cytotoxic and molecular targeted drugs ($N = 3$)	Total ($N = 55$)
Neutropenia	5 (16%)	1 (5%)	1 (33%)	7 (13%)
Leukocytopenia	3 (10%)	1 (5%)	1 (33%)	5 (9%)
Anemia	5 (16%)	3 (14%)	1 (33%)	9 (16%)
Thrombocytopenia	3 (10%)	3 (14%)		6 (11%)
Febrile neutropenia	1 (3%)			1 (2%)
Nausea	1 (3%)			1 (2%)
Anorexia	1 (3%)		1 (33%)	2 (4%)
Diarrhea	1 (3%)			1 (2%)
Small intestinal mucositis	1 (3%)			1 (2%)
Enterocolitis infection	1 (3%)			1 (2%)
Colonic hemorrhage	1 (3%)			1 (2%)
Rectal ulcer	1 (3%)			1 (2%)
Skin-related toxicities			1 (33%)	1 (2%)
Peripheral sensory neuropathy			1 (33%)	1 (2%)
Stroke		1 (5%)		1 (2%)
Pneumonitis	1 (3%)	2 (10%)		3 (5%)
Sepsis	1 (3%)			1 (2%)

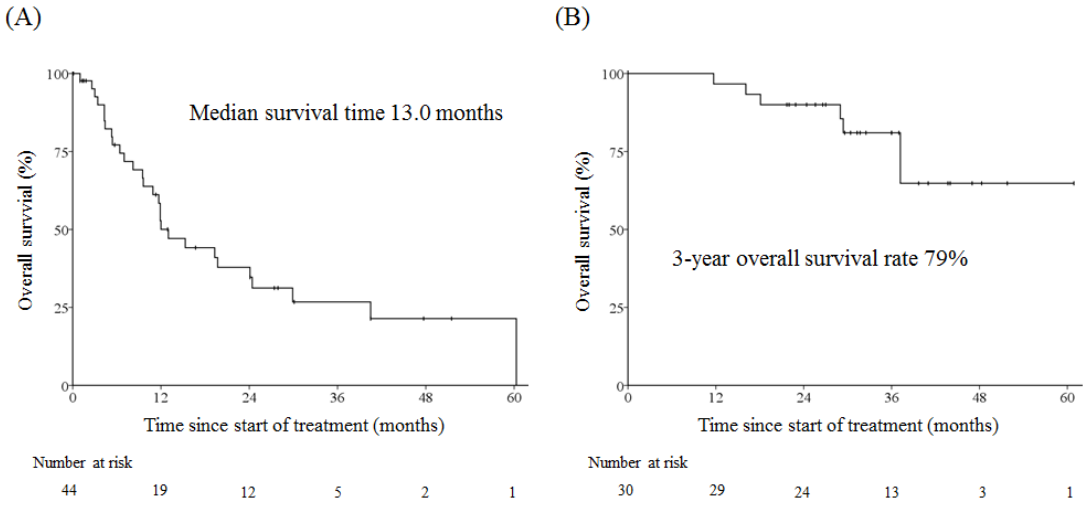
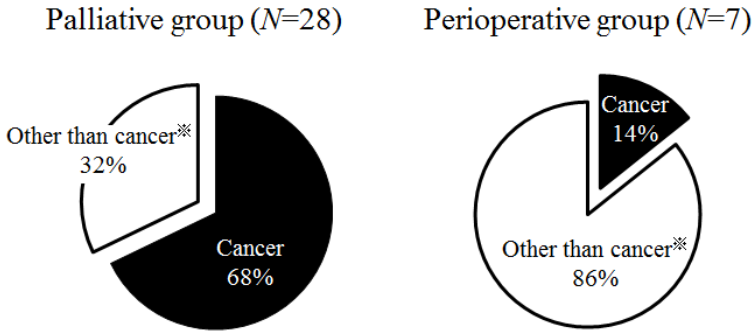


Figure 1. Kaplan–Meier curves for overall survival. (A) Palliative group (B) Perioperative group



※Details of cause of death other than cancer

Cause of death other than cancer	Palliative group (*N*=9)	Perioperative group (*N*=6)
Infection	2	2
Sudden death	2	2
Heart failure	2	
Intestinal perforation	1	
Cerebral infarction		1
Unknown	2	1

Figure 2. Cause of death

Supplementary Figure 1.