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Correlation between Overall Survival and Hospitalization- or Outpatient Consultation-Free Period in Patients Treated with Palliative Chemotherapy: Comparison of Incurable Gastric Cancer and Pancreatic Cancer

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Abstract

Introduction: Although the key outcomes of palliative chemotherapy are overall survival (OS) and quality of life (QOL), frequent hospitalization and outpatient consultation may worsen the QOL of patients with advanced cancer.

Methods: We retrospectively evaluated 101 patients with incurable gastric or pancreatic cancer. The length of hospitalization (LOH) and the outpatient consultation time (OCT) were combined for the clinical course duration. Hospital-free survival (HFS) was obtained by subtracting the LOH and OCT from OS.

Results: A strong correlation was observed between OS and OCT and between OS and HFS in patients with gastric and pancreatic cancer. A significant difference between OS and HFS was observed in patients with gastric cancer; conversely, no such differences were observed in pancreatic cancer patients.

Conclusion: Patients devoted about 10% of their OS to hospitalization and outpatient consultation. Future clinical trials for palliative chemotherapy with HFS, similar to OS, as a key outcome are warranted.

Keywords: Advanced cancers; Chemotherapy; Gastric neoplasms; Palliative therapy; Pancreatic neoplasms; Retrospective study

Introduction

The main objectives of palliative chemotherapy are to prolong survival and maintain a good quality of life (QOL). Although the approach to palliative chemotherapy differs considerably depending on the doctor's expertise, most medical oncologists recommend aggressive chemotherapy [1, 2]. When explaining palliative chemotherapy to patients with incurable cancer, oncologists present the results of clinical trials; this includes survival benefit with an endpoint [3, 4], as well as the side effects based on the Common Terminology Criteria for Adverse Events [5]. However, in actual clinical settings, 'oncologists' attention is focused on palliative chemotherapy rather than on best supportive care [2]. Typically, QOL is evaluated using several types of questionnaires that depend primarily on patient subjectivity [6,7]. Therefore, it is challenging to consecutively administer self-rating evaluations from the beginning of palliative chemotherapy till death. While patients tend to regard the median overall survival (OS) as the time left for themselves, the OS duration is often not spent at their discretion. The QOL deteriorates significantly in the terminal stage, in which hospitalization is often required [8]; palliative chemotherapy might, thus, lead to frequent hospitalization and outpatient consultation. No matter how long the OS achieved by palliative chemotherapy is, this could adversely affect QOL.

An estimation of the individual OS is not sufficiently accurate in patients with incurable cancer, leading to difficulty in decision-making regarding treatment [9]. Extended hospital stays and frequent hospital visits are generally considered to have adverse effects on patients' QOL; therefore, more clinical information that could affect the qualitative aspects of OS could be useful to help patients with the decision-making process for treatment [10].

In other countries, many cancer patients undergo chemotherapy in specialized hospitals, receive treatment for moderate symptoms in general practitioners' clinics, and receive end-of-life care in hospices or their homes. Therefore, obtaining an accurate length of hospitalization (LOH) and OCT from the beginning of palliative chemotherapy to death is difficult. Conversely, in Japan, patients with cancer are less likely to receive treatment interventions by general practitioners. Their deaths occur less often at hospices or their homes.

In general, patients with inoperable gastric and pancreatic cancer have similarly poor prognoses among the malignant tumors of the gastrointestinal tract. The standard chemotherapy regimen differs between these two malignat tumors, leading to differences in LOH and OCT throughout these patients' clinical courses.

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Therefore, it was considered that there may be a difference in QOL between gastric cancer patients and pancreatic cancer patients.

Materials and Methods

We retrospectively evaluated patients with incurable gastric or pancreatic cancer for local invasion or distant metastases with an Eastern Cooperative Oncology Group performance status of 0-2 (incurable) who were admitted to the Miyagi Cancer Center (Natori, Japan) between May 1, 2014, and December 31, 2018, and died on or before December 31, 2019. The only exclusion criterion is the absence of palliative chemotherapy.

We collected data on sex, age, disease spread, place of death, and OS. The LOH and OCT were combined for the entire clinical course duration, and HFS was obtained by subtracting the LOH and OCT from OS. OCT included outpatient chemotherapy visits, treatment for adverse effects, and routine examinations such as computed tomography and endoscopy. To evaluate the qualitative aspects of OS, we introduced hospital-free survival (HFS) as a new outcome; this was defined as the period without either hospitalization or outpatient consultation. We analyzed the relationship between OS, LOH, OCT, and HFS; the raw data are shared in Figshare (https://doi.org/10.6084/m9.figshare.13204256.v1).

Statistical analyses

Differences between gastric and pancreatic cancer according to age (≤70 years *vs*. >70 years), sex, disease spread (locally advanced, ascites, liver metastasis, lung metastasis), and place of death (hospital or home) were evaluated using logistic regression analyses; a two-tailed $P<0.05$ was considered significant. The correlations between OS and LOH, OS, and OCT, and OS and HFS were examined using scatter plots; a coefficient of determination ≥0.5 was considered a strong correlation, whereas $0.5>r^2\geq0.1$ was considered a moderate correlation. OS and HFS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using Statistical Package for the Social Science V24 (SPSS Inc., Chicago, IL, USA).

The ethics committee of Miyagi Cancer Center approved this study (approval number 4). All procedures were performed following the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

According to the local ethics policy for retrospective analysis of our own anonymized clinical data, information about this study and an opt-out method were provided on a website. Informed consent was obtained from all patients or their families. Therefore, participants did not provide written or verbal consent.

Results

As shown in table 1, 101 patients with gastric and pancreatic cancer were enrolled. Liver and lung metastases were more prevalent in patients with pancreatic cancer than in those with gastric cancer [liver metastases (+/-): pancreatic cancer (20/31) vs. gastric cancer (12/38); $P<0.05$; lung metastases (+/-): pancreatic cancer (10/41) vs. gastric cancer (1/49);$P<0.01$]. There were no differences in sex, age (≤70 years vs. >70 years), the existence of locally advanced cancer and ascites, and place of death (hospital vs. home) between gastric cancer and pancreatic cancer patients.

The correlation between OS and LOH was examined using a scatter plot analysis. In gastric cancer patients, a moderate correlation was observed between OS (x-axis) and LOH (y-axis) (coefficient of determination: $r^2=0.251$, $y=55.4+0.07x$); however, no correlation was seen in patients with pancreatic cancer ($r^2=0.048$, $y=50.2+0.03x$) (Figure 1). A weak correlation was observed between OS and the LOH among patients who died in hospitals ($r^2=0.212$, $y=48.3+0.07x$); however, no correlation was noted in patients who died at home ($r^2=8.50x10\text{-}4$, $y=66.6+0.004x$) (Figure 2). A strong correlation was found between OS and OCT in patients with gastric cancer ($r^2=0.870$, $y=5.1+0.08x$) and those with pancreatic cancer ($r^2=0.722$, $y=4.3+0.08x$) (Figure 3); similarly, a strong correlation was observed between OS and HFS both in patients with gastric ($r^2=0.973$, $y=50.3+0.85x$) and pancreatic cancer ($r^2=0.981$, $y=46.0+0.89x$) (Figure 4).

However, there was a significant difference between OS and HFS in gastric cancer patients (median survival: 13.8 vs. 10.0 months; $P<0.05$) (Figure 5); conversely, there was no significant difference between OS and HFS in pancreatic cancer patients (median survival: 11.4 vs. 8.6 months;$P=0.102$) (Figure 6).

Discussion

There are two specific points to note in this study: first, OS, LOH, and OCT were investigated from the start of palliative chemotherapy till death in patients with incurable gastric cancer and pancreatic cancer; second, HFS, defined as the period without hospitalization and outpatient consultation, was introduced as a new indicator of the qualitative aspects of OS. Strong correlations between OS and OCT, and between OS and HFS, were observed in the patients with gastric cancer and pancreatic cancer; however, using a Kaplan–Meier analysis, a significant difference was only observed between OS and HFS in the patients with gastric cancer.

Reasons for hospitalization may include chemotherapy-related and unrelated causes that arise from either an underlying cancer diagnosis or a noncancer diagnosis [11, 12]; most patients die during hospitalization [13].In this study, a moderate correlation between OS and LOH was observed in patients with gastric cancer but not in patients with pancreatic cancer; LOH was insignificant compared to OS in gastric cancer patients. These results could be explained by the heterogeneity in disease progression, therapeutic effects, and side effects of chemotherapy in patients[14].

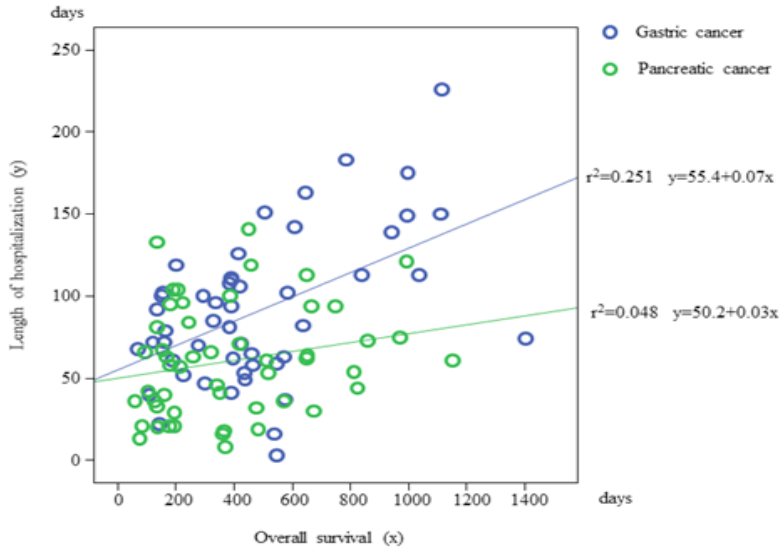

Figure 1: Correlation between overall survival and the length of hospitalization in patients with gastric cancer and pancreatic cancer

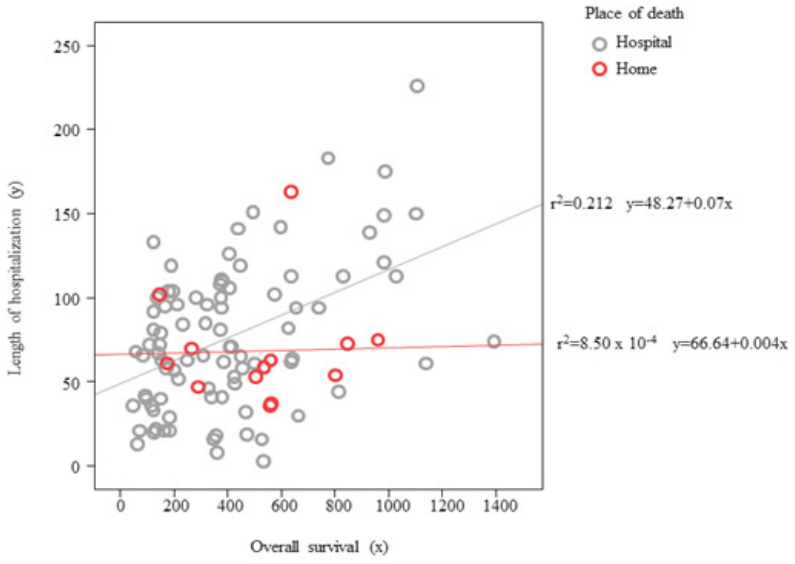

Figure 2: Correlation between overall survival and the length of hospitalization in patients who died at home or in the hospital

Table 1: Multivariate logistic regression analysis of incurable gastric and pancreatic cancer

Variable	Gastric cancer	Pancreatic cancer		Odds ratio (95% confidence interval)	P-value
	(n=50)	(n=51)	(n =101)		
Sex					
Female	16 (32.0%)	20 (39.2%)	36 (35.6%)	1.78 (0.70-4.48)	0.224
Male	34 (68.0%)	31 (60.8%)	65 (64.4%)	1.00 (ref.)	
Age					

<70	32 (64.0%)	31 (60.8%)	63 (62.4%)	0.56 (0.23-1.39)	0.213
≥70	18 (36.0%)	20 (39.2%)	38 (37.6%)	1.00 (ref.)	
Spread of disease					
Locally advanced cancer					
(-)	34 (68.0%)	38 (74.5%)	72 (71.3%)	0.35 (0.10-1.20)	0.95
(+)	16 (32.0%)	13 (25.5%)	29 (28.7%)	1.00 (ref.)	
Ascites					
(-)	41 (82.0%)	40 (78.4%)	81 (80.2%)	0.41 (0.12-1.39)	0.152
(+)	9 (18.0%)	11 (21.6%)	20 (19.8%)	1.00 (ref.)	
Liver metastases					
(-)	38 (76.0%)	31 (60.8%)	69 (68.3%)	0.24 (0.08-0.76)	<0.05*
(+)	12 (24.0%)	20 (39.2%)	32 (31.7%)	1.00 (ref.)	
Lung metastases					
(-)	49 (98.0%)	41 (80.4%)	90 (89.1%)	0.03 (0.00-0.30)	<0.01*
(+)	1 (2.0%)	10 (19.6%)	11 (10.9%)	1.00 (ref.)	
Place of death					
Hospital	42 (84.0%)	46 (90.2%)	88 (87.1%)	1.74 (0.46-6.59)	0.413
Home	8 (16.0%)	5 (9.8%)	13 (12.9%)	1.00 (ref.)	

*$P<0.05$

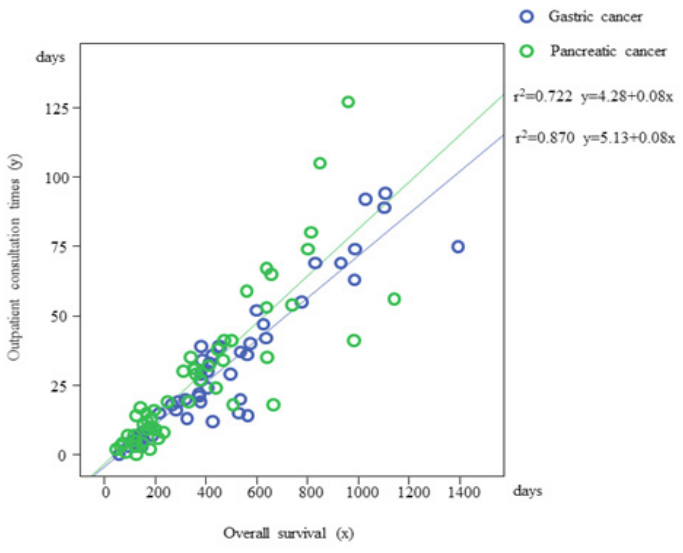

Figure 3: Correlation between overall survival and outpatient consultation times in patients with gastric cancer and pancreatic cancer

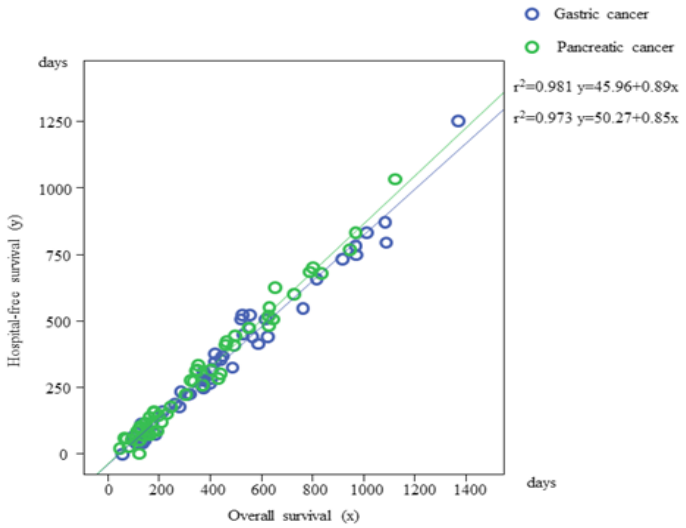

Figure 4: Correlation between overall survival and hospital-free survival in patients with gastric cancer and pancreatic cancer

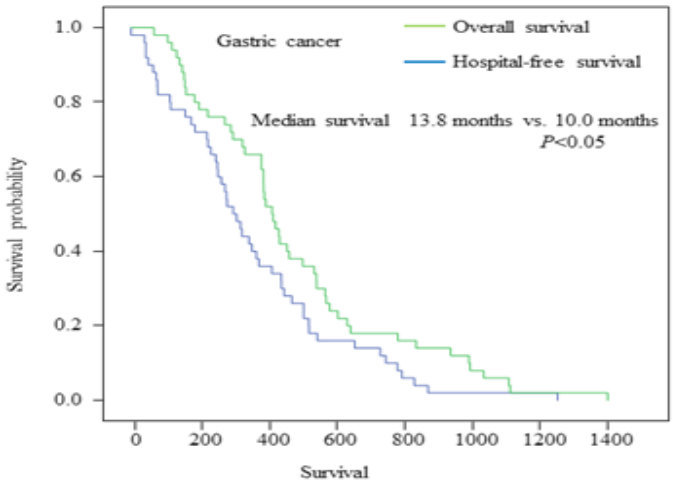

Figure 5: Kaplan–Meier curves of the overall survival and hospital-free survival of patients with gastric cancer

The strong correlation between OS and OCT observed in patients with gastric cancer, and pancreatic cancer was likely due to OS's extension, attributed to palliative chemotherapy; however, this was considered to induce frequent outpatient consultation.

Severe symptoms that require hospital admission are reported to affect QOL adversely [15]. At present, palliative chemotherapy is mostly administered in an outpatient setting[16]; however, frequent outpatient consultation for chemotherapy may burden patients with advanced cancer with only a limited amount of time left [17]. In prior studies, LOH had only been analyzed for a certain period, rather than for the entire duration of the clinical course [18-21]; therefore, no studies have reported OCT throughout the clinical course of patients with advanced cancer.

In our study, we defined HFS as the period without hospitalization and outpatient consultation for the qualitative aspect of OS. A strong correlation between OS and HFS was similarly observed in both patients with gastric and pancreatic cancer; the tilt of the regression line indicated that about 10% of the OS represented the period of hospitalization and OCT.

Despite the patient background variation, systematic reviews regarding palliative chemotherapy have reported that a median OS of 14 months will yield the best result in patients with incurable gastric cancer [22]. In patients with pancreatic cancer, the median OS was 11.1 months with FOLFIRINOX [23] and was shorter with other regimens [24]. Generally, the prognosis of patients with gastric cancer is slightly better than that of those with pancreatic cancer; however, there was no significant difference in the median OS between patients with gastric and pancreatic cancer observed in this study. Patients with pancreatic cancer having lung metastases were reported to have better

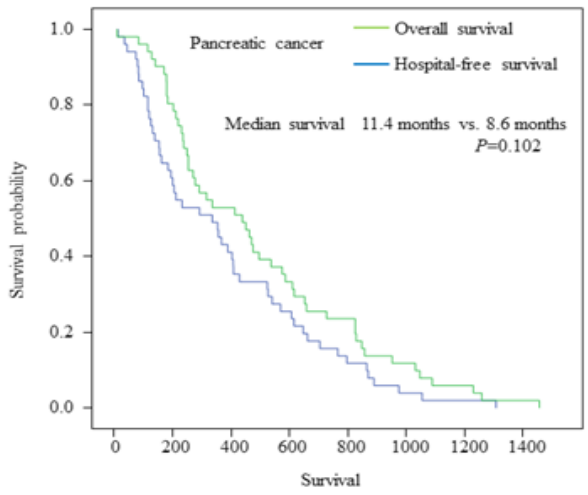

Figure 6: Kaplan–Meier curves of the overall survival and hospital-free survival of patients with pancreatic cancer

prognoses. In this study, 20% of the patients with pancreatic cancer had lung metastases [25].

Our study indicated no significant difference between OS and HFS in patients with pancreatic cancer; however, a significant difference was observed in gastric cancer patients. These imply that gastric cancer patients tend to dedicate more time toward hospitalization and outpatient consultation than pancreatic cancer patients do.

The critical outcome of cancer chemotherapy in clinical trials is survival benefits [26]; other results are the side effects of chemotherapy and QOL. In clinical practice, patients with a good performance status are recommended a subsequent round of treatment after failure of the first chemotherapy line [27, 28]. Therefore, QOL and the side effects of chemotherapy in a clinical trial are not indicative of the entire clinical course. At present, a comprehensive outcome describing the qualitative aspects of OS does not exist; therefore, we introduced HFS as a surrogate outcome to evaluate the qualitative aspects of OS in our study.

Decision-making for the mode of treatment in advanced cancer is hard for both patients and oncologists [29, 30]. For decision-making, the disease course, symptom, and prognosis are essential [2]. However, only half of the oncologists are reported to show specific OS data to patients [31, 32]; thus, patients may not be comprehensively informed. In contrast, patients tend to emphasize the length of life more than the QOL and prefer palliative chemotherapy over Best Supportive Care [33]. Patients should know that both OS and HFS are periods determined at their discretion, guiding treatment decision-making.

This study was limited by its retrospective nature and small sample size, including only gastric and pancreatic cancer patients. Long term retrospective study for a large sample size might affect LOH, OCT, and OS by newly introduced palliative chemotherapy.

A strong correlation was observed between OS and OCT, as well as OS and HFS in patients with gastric and pancreatic cancer. Patients with advanced-stage cancer devoted about 10% of their OS to hospitalization and OCT.

Conclusion

A difference in correlation between the OS and HFS was observed in patients with gastric cancer and pancreatic cancer. Patients with advanced gastric and pancreatic cancer should be informed that palliative chemotherapy requires hospitalization and an OCT equivalent to 10% of their expected OS. Thus, future clinical trials for palliative chemotherapy with HFS, similar to OS, as a critical outcome are warranted.

Statements

Statement of Ethics

Ethics approval: The ethics committee of Miyagi Cancer Center approved this study (approval number 4). All procedures were performed according to the institutional and national research committee's ethical standards and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate: According to the local ethics policy for the retrospective analysis of our own anonymized clinical data, informed consent with opt-out was obtained from all patients.

Author's Contributions

All authors made substantial contributions to the conception and design of this study. KO collected medical data, and YM analyzed these data and drafted the manuscript. All authors revised it critically for important intellectual content and gave final approval on the version to be published.

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