Relationship between the response to treatment and the prognosis of patients with aggressive lymphomas treated with chemotherapy followed by involved-field radiotherapy :Radiographic assessment

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Running title: Early response and prognosis in NHL

CONFLICT OF INTEREST STATEMENT:

The authors indicated no potential conflicts of intrest.

Abstract

Background: We examined the relationship between the response to treatment and prognosis of patients with aggressive lymphoma.

Methods: We reviewed 33 patients with aggressive lymphoma treated with chemotherapy consisting of the CHOP regimen followed by radiotherapy. Twelve patients had Stage I, 13 had Stage II, 6 had Stage III, and 2 had Stage IV disease. According to the International Prognostic Index (IPI), 13 had low, 15 had low-intermediate, 2 had high-intermediate, and 3 had high IPI. After three to six cycles of chemotherapy, involved-field radiotherapy was performed. We evaluated the response to treatment by computed tomography (CT), magnetic resonance imaging (MRI), and Gallium scintigraphy (Ga-67) at the time of completion of chemotherapy and the time of completion of radiation therapy. The median follow-up period was 48 months (4–80).

Results: The 2-year progression-free survival rates of the patients with Ga-67 positive uptake and Ga-67 negative uptake after completion of chemotherapy were 78% and 26% (p = .009), respectively. However, there were no statistically significant correlations between progression-free survival and the response after completion of

chemotherapy determined by CT (p = .75) or MRI (p = .19). The response to treatment at the time of completion of overall treatment was not useful for prediction of prognosis.

Conclusions: Ga-67 positive uptake at the completion of chemotherapy before radiotherapy may be associated with poor prognosis.

Mini Abstract

Ga-67 scintigraphy at the completion of chemotherapy is an efficient method for predicting the outcome of aggressive lymphoma treated with chemotherapy consisting of the CHOP regimen followed by radiotherapy.

Key words: aggressive lymphoma, chemotherapy, radiotherapy, Gallium scintigraphy

Introduction

The treatment policy for aggressive lymphoma is determined based on the International Prognostic Index (IPI)[1], Cotswolds Modification of the Ann Arbor Staging System[2], and patient's condition. Patients with localized aggressive lymphoma can be cured with systemic chemotherapy and/or radiotherapy. The CHOP regimen (consisting of a combination of Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) is generally the first choice for chemotherapy[3] with and without consolidative radiotherapy[4]. However, the usefulness of rituximab (anti-CD20 monoclonal antibody) has been reported and R-CHOP (CHOP + rituximab) has been adopted for chemotherapy[5]. With these standard treatments, the cure rate of patients with all stages of aggressive lymphoma is about 40%. However, there are limits to predicting the outcome based on IPI score, and further prognostic predictors during treatment leading to early changes in therapy may improve outcome and survival.

With regard to the role of imaging diagnosis of malignant lymphoma, imaging evaluation contributes to not only differential diagnosis but also to the initial staging for determining the optimum treatment strategy and evaluation of the effects of treatment. The International Workshop to Standardize Response Criteria based on computed

tomography (CT) have been widely used for response assessment of Non-Hodgkin's lymphoma (NHL)[6]. CT and Gallium scintigraphy (Ga-67) are generally used for evaluation of the effects of treatment in patients with NHL. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are also used in special situations. However, the values of these modalities for clinical usage are still controversial. This raises questions of how best to make use of the results of CT, MRI, and Ga-67 to make changes to the treatment strategy.

We evaluated the relationship between the response to treatment evaluated by radiographic imaging and prognosis of patient with aggressive lymphoma.

Material and Methods:

We reviewed 33 patients with aggressive lymphoma treated with chemotherapy followed by radiotherapy from 2000 to 2003. The median age of the patients was 64 years (range, 20–81), and the male:female ratio was 12:21. Pathological diagnosis was confirmed according to the World Health Organization Classification[7] of lymphoid neoplasms: 26 patients were classified as having lesions of diffuse large B-cell

lymphoma, 2 as peripheral T-cell lymphoma, 2 as angioimmunoblastic T-cell lymphoma, and 3 as extranodal T-/NK-cell lymphoma (Table 1). Thirteen percent of patients (4/33) were in performance status 2–3, 68% (19/33) had elevated serum lactate dehydrogenase, and 21% (7/33) had bulky tumors (>6 cm). According to the Cotswolds modification of the Ann Arbor staging system[2], pretreatment evaluation included history and physical examination, complete blood count, serum chemistry, upper gastrointestinal endoscopy, bone marrow aspiration, CT scan of the neck, chest, abdomen, and pelvis, Ga-67, MRI of the primary lesion, and ultrasonography of the neck and abdomen. The median follow-up period for all patients was 21 months (range, 4–46).

CT was performed with a slice thickness of 5mm before and after the intravenous injection of contrast medium. MRI was performed with a 1.5-T unit using spin-echo technique. T1-weighted images were acquired axial images. Axial T2-weighted fat-suppressed images were also obtained. Slice thickness was 5 mm with no interslice gap in the axial projection. Thereafter, T1-weighted post gadolinium with fat-suppressed images in axial projections were obtained sequentially. Ga-67 scanning was performed 48-72 hr after intravenous injection of 185 MBq ^{67}Ga-citrate. SPECT cameras with medium-energy, general-purpose collimators and three energy peaks of 93,

184 and 296 keV were used. Total-body images in anterior and posterior views were supplemented with appropriate planar views of the thorax and abdomen. After uniformity correction, 10 mm transaxial tomograms were reconstructed using a medium filter.

Treatment

Chemotherapy consisted of the CHOP regimen, including cyclophosphamide at 750 mg/m^2 (day 1), doxorubicin at 50 mg/m^2 (day 1), vincristine at 1.4 mg/m^2 (day 1), and oral prednisolone at 100 mg/day (days 1–5). Drug doses were reduced by up to 50% in consideration of age and co-morbid illness; full-dose CHOP was applied in 22 patients, 80% CHOP in 9 patients, 70% CHOP in 1 patient, and 50% CHOP in 1 patient. Chemotherapy was repeated every three weeks. The number of treatment cycles was determined by prognostic factors, such as stage, IPI score, and tumor size. In patients in clinical stage I–II, with IPI score of 0–2, or with non-bulky tumors (≤ 6 cm), three cycles of CHOP were used. Six cycles were applied in other patients in Stage III–IV, with IPI score of 3–5, or with bulky tumors (>6 cm). Three cycles of CHOP were applied in 24 patients and 6 cycles in 8 patients. One patient received 4 cycles of treatment because of progressive disease.

After completion of three to six cycles of chemotherapy, involved-field radiotherapy was performed to all patients. The involved field was defined as the regional area including the primary lesion and involved nodes. In patients in Stage III-IV, radiation field was determined by the primary bulky lesion. Conventional radiotherapy was used with super-voltage X-rays (4–10 MV). The radiation dose was 30–30.6 Gy given in 17–20 fractions over 4 weeks in patients who achieved complete response, and 40–50 Gy in 20–28 fractions over 4–6 weeks in patients who did not achieve complete response.

Response assessment

CT, MRI, and Ga-67 were used for imaging diagnosis of the lesions. Evaluation was performed pre-treatment, after chemotherapy within the 4 weeks, and at the end of radiation therapy within 4 weeks. Post-treatment MRI was omitted in 3 patients with complete disappearance of primary lesion on CT. The response to treatment was determined by CT and MRI according to the report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma[6]. Complete response (CR) was defined as complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms. Previously

involved nodes or nodal masses on CT or MRI more than 1.5 cm in largest diameter must regress to less than 1.5 cm and previously involved nodes/nodal masses of 1.1 to 1.5 cm must regress to less than 1.0 cm. Partial response (PR) was defined as a reduction of at least 50% in the sum of the product of the greatest diameters of the six largest dominant nodes or nodal masses with no increase in the size of other nodes and with no new sites of disease. Stable disease (SD) was less than PR but not progressive disease (PD). PD was defined as a 50% increase in the sum of the product of the greatest diameters from the nadir of any previously identified abnormal node for PR and non-responders, or the appearance of any new lesion during or at the end of therapy. Ga-67-based determinations of CR, SD, and PD were defined as complete disappearance of accumulation, equal accumulation, and increased accumulation as compared with before treatment, respectively.

Statistical analysis

Survival was measured from the first day of treatment. Death from any cause was included as an event in the overall survival, and any failure and any cause of death were included as events in the progression-free survival. The overall and progression-free survival curves were calculated using the Kaplan-Meier method[8]. Differences between

the survival rates were tested for statistical significance by the generalized Wilcoxon test. Statistical significance for all analyses was set at $p < .05$.

Results

After completion of treatment, 21 patients (64%) achieved CR, 7 patients (21%) achieved PR, and 5 patients (15%) developed PD of the 28 patients showing CR and PR, 21 showed no progression, while the remaining 7 did show progression. One patient had relapse at local progression and 6 patients showed relapse at lymph nodes outside the area of the primary lesion.

The 2-year overall and progression-free survival rates were 72% and 63%, respectively (Figure 1). The 2-year progression-free survival rates in patients with IPI scores of 0–1 and 2–4 were 92% and 49%, respectively ($p = .001$). The correlation between progression-free survival and response after completion of chemotherapy was stronger with Ga-67 ($p = .009$) than CT or MR (Table 2), neither of which showed statistically significant correlations ($p = .75$ and $p = .19$, respectively). No correlations were found between the response after completion of all treatments and progression-free survival with CT ($p = .15$), MRI ($p = .77$), or Ga-67 ($p = .23$).

The 2-year progression-free survival rate in patients in whom Ga-67 uptake had disappeared at completion of chemotherapy was 80%, while that in patients in whom uptake remained was 26% (p = .001) (Figure 2).

Discussion

Aggressive lymphomas are a heterogeneous group of diseases that are various with regard to histopathology, clinical behavior in response to therapy, and outcome. In contrast to many solid tumors, lymphomas are highly sensitive to chemotherapy and radiotherapy, and about 50–60% of patients with aggressive lymphoma achieve prolonged survival and cure[9, 10]. In the present study, 21 of 33 patients (63%) with aggressive lymphoma achieved disease-free survival for the duration of the study.

In the past, determination of the effects of treatment for malignant lymphomas is based on CT[6]. However, there are limitations in assessment of response to therapy by CT[11–15], and Ga-67, FDG-PET, and MRI have been reported to be useful for detection of lesions. MRI is particularly useful in identifying bone and CNS involvement. MRI can suggest leptomeningeal involvement when gadolinium has been used. MRI can also be used to identify bone marrow involvement[16]. In contrast, CT and MRI often show a

residual mass, which may not be neoplastic. In clinical CR patients treated with chemotherapy and/or radiation, only 10–18% of residual masses detected by CT and/or MRI are viable tumors[17, 18]. In cases in which residual masses were detected by CT or MRI, it was difficult to discriminate between a viable tumor, necrosis, and fibrosis. The response to treatment of aggressive lymphoma is heterogeneous, even in patients with the same histological findings. Ga-67 and FDG-PET findings are indicators of cancer cell viability and can be used to monitor the response of the tumor cells in each patient to the particular course of chemotherapy received. In Hodgkin's lymphoma and aggressive or highly aggressive lymphoma, Ga-67 and FDG-PET may prove particularly useful in detecting residual disease[11–15, 19-21]. It has been shown previously that Ga-67 performed at the end of chemotherapy is superior to CT in patients with both Hodgkin's lymphoma and NHL for monitoring the response to treatment[12, 22, 23].

After patients have completed the entire planned treatment regimen, reevaluation should be done to determine the response to therapy. Achieving complete remission to therapy is the most important single prognostic factor in patients with NHL. Salvage treatment, such as high-dose therapy and autologous or allogeneic bone marrow transplantation, can sometimes cure disease in patients who fail to respond to initial therapy[24]. In the relationship between treatment effect and prognosis, patients who react

early to chemotherapy are predisposed to accomplish a high CR rate[25, 26]. Kaplan *et al.* [11] reported Ga-67 imaging to be an excellent indicator of residual viable tumors early during chemotherapy in 37 patients with diffuse large B-cell lymphoma. At follow-up, 59% of the patients who were Ga-67 positive halfway through therapy died, whereas in the group of negative patients only 20% died due to disease progression. Front *et al.*[12] compared the disease-free survival between patients with positive or negative Ga-67 and CT scan. CT findings were not predictive of outcome in contrast to Ga-67 imaging. In the present study, the correlation between progression-free survival and response after completion of chemotherapy was stronger in determination by Ga-67 than by CT.

The value of FDG-PET in the assessment of lymphoma has been investigated. FDG-PET combines the advantages of nuclear medicine techniques, such as Ga-67, as an indicator of tumor viability with improved resolution and higher sensitivity, and these advantages lead to higher lesion detection efficiency. In cases in which the persistence of accumulation was seen with FDG-PET after 1 cycle of chemotherapy for Hodgkin's and non-Hodgkin's lymphoma, prognosis was wrong[15, 27, 28]. On the other hand, in cases with disappearance of accumulation after one cycle of chemotherapy, the recurrence rate was reduced. Similarly, early interim FDG-PET is an accurate and independent predictor of progression-free survival and overall survival[29-35]. All studies

published to date suggested increased sensitivity of FDG-PET as compared with other imaging modalities, including Ga-67, when used for lymphoma staging[36-39]. Such findings provided rationale for incorporating FDG-PET into revised response criteria for malignant lymphoma[40-42]. PET is strongly recommended before treatment for patients with routinely FDG-avid, potentially curable lymphomas to better delineate the extent of disease. In addition, FDG-PET is essential for the post-treatment assessment of diffuse large B-cell lymphoma and Hodgkin's lymphoma[42]. Although it has been shown that Ga-67 and FDG are both viable agents and that they show similar behavior in lymphoma after treatment, FDG-PET has significantly higher cost and more complicated logistics than Ga-67. Just now Ga-67 scan should be used as alternative of PET in hospitals where it has not been set up.

The results of the present study suggest that FDG-PET and Ga-67 scintigraphy are an efficient method for predicting the outcome of individual patients with aggressive lymphoma. Patients with abnormal FDG-PET or Ga-67 uptake after chemotherapy may need to receive additional treatment modifications. Effort is now being made to improve the outcome in patients who do not achieve complete response, including modification of dose intensity, use of autologous stem cell transplantation, and multiple new agents. Further studies are required to determine whether early selection with FDG-PET or

Ga-67 increases survival in patients whose conditions do not show an early response to treatment.

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Figure Legends

Figure 1

Overall and progression-free survival curves of all patients

Figure 2

Progression-free survival curves according to the findings of Gallium scintigraphy after completion of chemotherapy

Table 1 Patients and tumor characteristics.

Age (years)		20–81 (median 64)
Sex		
	Male	12
	Female	21
WHO Classification		
	Diffuse large B-cell	26
	Peripheral T-cell	2
	Angioimmunoblastic T-cell	2
	Extranodal T-/NK-cell	3
Stage		
	I	12
	II	13
	III	6
	IV	2
IPI		
	Low	13
	Low-intermediate	15
	High-intermediate	2
	High	3
Primary site		
	Waldeyer’s ring	12
	Lymph node	8
	Sinonasal cavity	6
	Thyroid	3
	Bone	3
	Soft tissue	1

Abbreviations: NK-cell, natural-killer cell; IPI, International Prognosis Index.

Table 2 Hazard ratios assessing for evaluation of the treatment effect by CT, MRI, and Ga-67 for progression-free survival

Modality	Hazard Ratios (95% CI)	*p* Value
After chemotherapy		
CT: CR	Reference	
CT: Residual	1.0 (0.3-4.7)	0.75
MRI: CR	Reference	
MRI: Residual	1.7 (0.6-16)	0.19
Ga-67: CR	Reference	
Ga-67: Residual	2.9 (1.7-40)	0.009
After chemotherapy followed by radiation		
CT: CR	Reference	
CT: Residual	0.2 (0-1.9)	0.15
MRI: CR	Reference	
MRI: Residual	0.5 (0-12)	0.77
Ga-67: CR	Reference	
Ga-67: Residual	1.5 (0.5-20)	0.23

Abbreviations: CR, Complete response; 95% CI, 95% confidence interval.

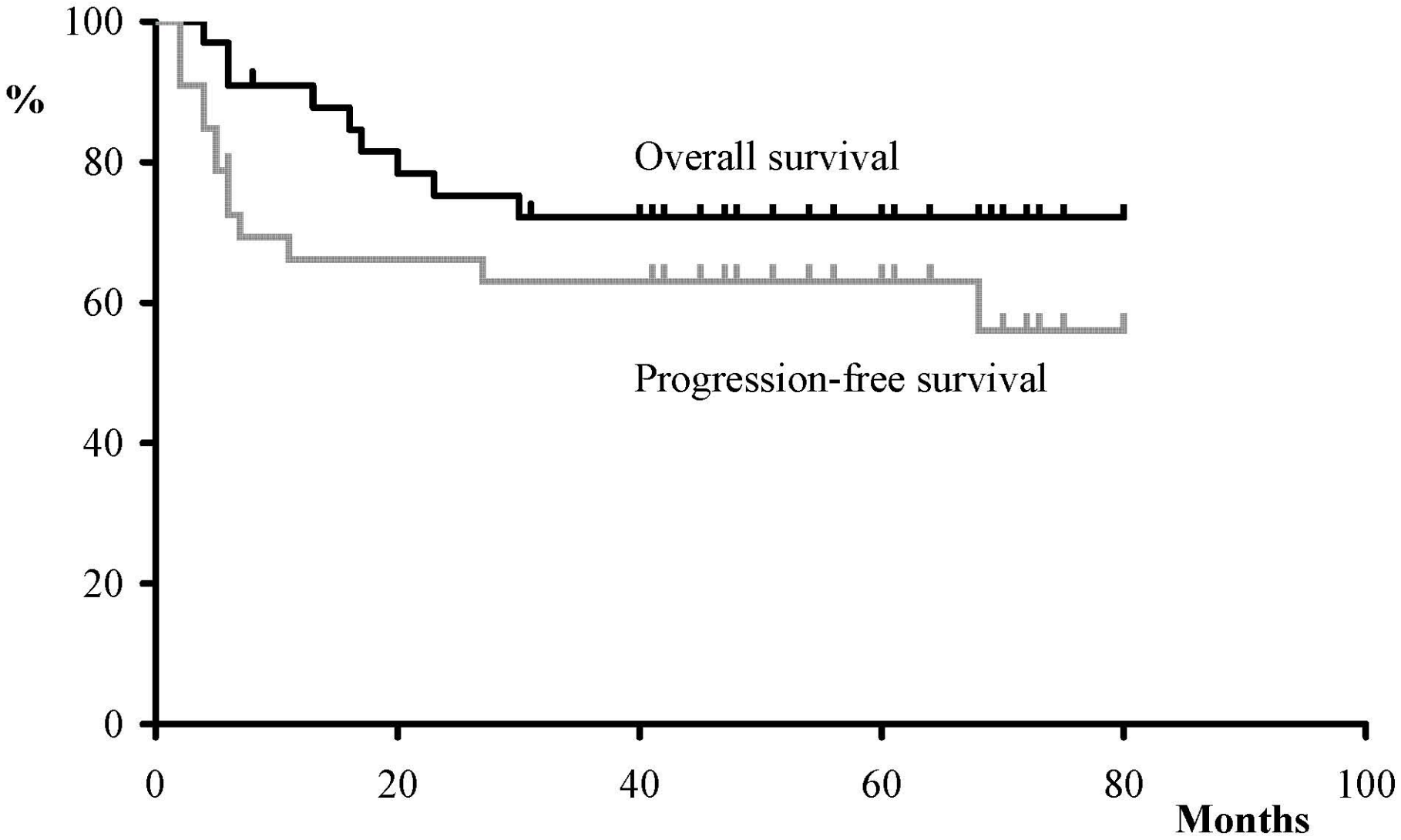
100
%
80
60
40
20
0
Overall survival
Progression-free survival
0
20
40
60
80
100
Months

Figure 1

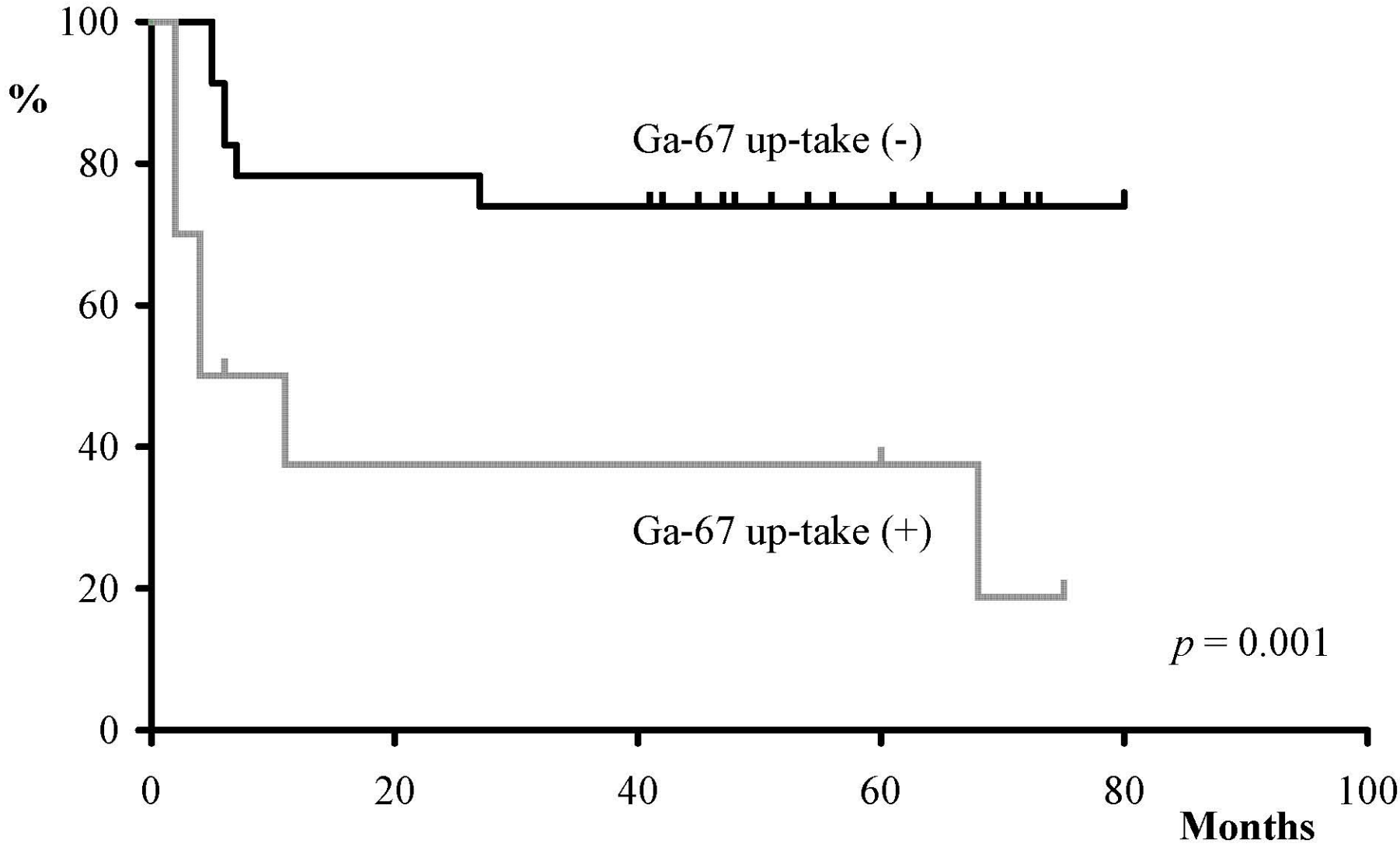
100
%
80
60
40
20
0
Ga-67 up-take (-)
Ga-67 up-take (+)
p = 0.001
0
20
40
60
80
100
Months

Figure 2