**Original Article**

# Clinical features and outcomes of 139 Japanese patients with Hodgkin lymphoma

**Authors:** Shinichi Makita[1, 4], Dai Maruyama[1], Akiko Miyagi Maeshima[2], Hirokazu Taniguchi[2], Ken-ichi Miyamoto[1], Hideaki Kitahara[1], Suguru Fukuhara[1], Wataru Munakata[1], Yukio Kobayashi[1], Jun Itami[3], and Kensei Tobinai[1, 4]

**Affiliations:** Department of [1]Hematology, [2]Pathology and Clinical Laboratory, and [3]Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan. [4]Course of Advanced Clinical Research of Cancer, Juntendo University Graduate School of Medicine, Tokyo, Japan.

**Running Title:** Treatment outcomes of HL in Japan

**Correspondence:** Dai Maruyama, MD, PhD.

Department of Hematology, National Cancer Center Hospital,

5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

Tel: +81-3-3542-2511

Fax: +81-3-3542-3815

E-mail: dmaruyam@ncc.go.jp

**Abstract**

Hodgkin lymphoma (HL) is a rare subtype of malignant lymphoma in Japan, and there are few reports of HL in Japan in recent years. We retrospectively analyzed the clinical features of 139 patients with HL who were diagnosed and treated at our institution between 1997 and 2011. The median age at diagnosis was 34 years with 83 male. Of these patients, 83 (60%) were early-stage and 56 (40%) advanced-stage. Seventy-three patients (88%) with early-stage disease received ABVd followed by irradiation. All of the 56 advanced-stage patients received chemotherapy, mainly ABVd. The 5-year progression-free survival (PFS) rates and overall survival rates were 90% and 94% in patients with early-stage disease, and 71% and 90% in those with advanced-stage disease. The PFS of patients with advanced-stage disease was significantly lower than those with early stage ($P = 0.014$). In conclusion, the outcomes of Japanese patients with HL in recent years were not improved as compared with the results of previous reports. We confirmed that patients with advanced-stage disease have lower PFS than those with early-stage disease. Prospective studies are needed to establish novel treatment strategies to improve the outcome of HL patients, especially those with advanced disease.

**Keywords:** Hodgkin lymphoma, ABVd, Japanese patient

## Introduction

Hodgkin lymphoma (HL) is one of the common subtypes of malignant lymphoma in Western countries [1, 2]. Although the patients with HL showed unsatisfied outcomes in1960s, the clinical development of radiotherapy and chemotherapy based on the several clinical trials in the past decades made HL a curable disease with favorable outcome [2].

In 1970s and 1980s, multi-agent regimen, MOPP (mechlorethamine, vincristine, procarbazine and prednisone) has been developed. Several trials reported the favorable response of MOPP regimen, while the toxicities such as sterility, premature menopause, and leukemogenesis were serious problems [3-5]. To solve these problems, the well-established multi-agent combination regimen, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) has been developed. ABVD with or without involved-field irradiation provides the best balance of effectiveness and minimization of toxicity and regarded as a standard of care in the patients with HL until recently [5, 6]. Although the optimal cycle of ABVD was controversial until early 2000s, 4 cycles of ABVD followed by irradiation was recommended in the early-stage HL, while 6 cycles of ABVD in the advanced-stage HL nowadays [7].

In Japan, HL is a rare subtype of malignant lymphoma; its incidence is approximately one-third of that in Western countries [8]. Therefore, Japanese trials for HL have been less frequently conducted. Three prospective studies for HL were conducted by the

Lymphoma Study Group of Japan Clinical Oncology Group (JCOG-LSG) from the1980s to 1990s [9-11]. Sequential phase II studies, JCOG8905 and JCOG9305 showed the safety and efficacy of C-MOPP/ABVd (cyclophosphamide, vincristine, procarbazine and prednisone/doxorubicin, bleomycin, vinblastine and dacarbazine) and ABVd regimens. Both regimens used a reduced dose of dacarbazine (250 mg/m$^2$) because of intolerable sever emesis related to dacarbazine in a polot study at that time [9]. As the 4-year progression-free survival (PFS) rate of the patients in JCOG8905 and the 5-year PFS rate in MOPP/ABVD in Cancer and Leukemia Group B (CALGB) study was 65.7% and 65%, respectively, ABVd regimen is supposed to have similar efficacy to original ABVD regimen in Japanese patients [7, 9]. The next phase II study, JCOG9705 investigated the ABV regimen, removing dacarbazine from ABVd, with an increased dose of doxorubicin [11]. The interim analysis revealed that the 2-year PFS with ABV was significantly inferior to that shown by ABVd in JCOG9305, suggesting that dacarbazine is a key agent for the treatment of HL. Based on these 3 studies, ABVd has been regarded as the standard of care in patients with previously untreated HL in Japan. There are few data about clinical characteristics and the outcomes of HL patients, except for the JCOG-LSG trials, especially in recent years. Therefore, this retrospective study was made to clarify the clinical characteristics and outcomes of the Japanese patients with HL

in recent years.

## Patients and Methods

### Patients

Among the 205 patients who were diagnosed as having HL at the National Cancer Center Hospital (NCCH) between September 1997 and December 2011, we retrospectively analyzed 139 consecutive patients who were initially treated in the setting of clinical practice at NCCH. All the histopathological diagnoses were made by experienced hemato-pathologists (AMM and HT) according to the WHO classification [12]. The protocol for this retrospective study was approved by the institutional review board of the National Cancer Center.

### Clinical staging

Clinical stage (CS) was determined according to the Ann Arbor classification system [13]. The extent of disease was assessed by chest X-ray, computed tomography (CT) scan from neck to pelvis, and bone marrow aspiration or biopsy. We determined CS I-IIA as early stage and CS IIB-IV as advanced stage. Bulky disease was determined by a mediastinal mass ratio > 0.33 on chest X-ray or a diameter larger than 10 cm on CT-scan. The

International Prognostic Score (IPS) was also assessed in patients with advanced stage disease [14].

Treatment strategy of HL in the present study

In 1990s and early 2000s, The patient with early-stage HL were treated according to the strategy of JCOG9305; the ABVd was scheduled to give 6 cycles or 7-8 cycles, when complete remission (CR) was obtained after 1-4 cycles or 5-6 cycles, respectively. The patient with bulky disease at initial presentation received irradiation after the ABVd. In the late 2000s, 4 cycles of ABVd followed by involved-field irradiation was performed regardless of bulky disease or interim-response.

The patients with advanced-stage HL were treated with 6-8 cycles of ABVd. The patiens with bulky disease or with residual disease after the ABVd received irradiation.

Statistical analysis

Response was assessed after completion of the initial treatment according to the International Workshop response criteria 1999 [15]. Among the patients who received [$^{18}$F] fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT, the response was assessed according to the revised response criteria for malignant lymphoma 2007 [16].

Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause. PFS was calculated from the date of diagnosis to the date of disease progression or death from any cause. OS and PFS were analyzed by the Kaplan-Meier method [17], with between-group comparisons made using log-rank tests. Multivariate analyses with a Cox proportional multiple regression model were performed to assess the impact of clinical determination on OS and PFS. A $P$ value $<0.05$ for a two-sided test was considered statistically significant. All statistical analyses were performed using Dr SPSS II software, release 11.0.1J (SPSS Japan, Tokyo, Japan).

## Results

### Patient characteristics

We analyzed a total of 139 HL patients, and their demographics and clinical characteristics are summarized in Table 1. Median age at diagnosis was 34 years (range, 14-83 years) with 83 male and 56 female patients. As a histologic distribution, 79 patients (57%) had nodular sclerosis (NS), 29 patients (21%) had mixed cellularity (MC), 5 patients (4%) had lymphocyte depletion (LD), 3 patients (2%) had lymphocyte rich (LR), and 12 patients (8%) had nodular lymphocyte predominant HL (NLPHL). Eleven patients (9%) had

classical HL, not otherwise specified. The performance status (PS) of the majority of patients was 0 or 1. Bulky disease was present in 31 patients (22%) and 28 of them had mediastinal bulky disease. Early stage and advanced stage were present in 83 (60%) and 56 (40%) patients, respectively. Among the advanced-stage patients, the numbers of patients with an IPS of 0-2 and 3 or higher were 32 (57%) and 24 (42%), respectively. In the present study, fourteen patients received high dose chemotherapy with autologous stem cell transplantation (HDC/ASCT) in first relapse. Five patients received allogeneic stem cell transplantation at the relapse after HDC/ASCT.

Initial treatments and responses

The details of the initial treatments and responses are shown in table 2. Among the 83 early-stage patients, 73 patients (88%) received chemotherapy followed by irradiation, while 22 (39%) of the 56 advanced-stage patients received chemotherapy followed by irradiation. The reasons for receiving irradiation after the chemotherapy in patients with advanced disease were as follows; clinical stage IIB (14 patients, 24%), initial bulky disease (4 patients, 8%), and residual disease after chemotherapy (4 patients, 8%). The overall response rates after the initial treatment in early-stage and advanced-stage were 97% and 93%,

respectively. Seventy-six early-stage patients (92%) achieved CR or CRu, while 46 (82%) advanced-stage patients achieved CR or CRu. Among the patients of all stages, 122 (87%) received ABVd therapy and the median number of cycles was 6 in early-stage and 8 in advanced-stage.

Toxicities

Table 3 lists the acute toxicities observed in the 122 patients who received ABVd therapy. The toxicities were assessed according to the criteria of NCI-CTCAE v4.0. The most frequent hematologic toxicity was neutropenia. Neutropenia with grade 3 and 4 was observed in 47 patients (39%) and 40 patients (33%), respectively. The most frequent non-hematologic toxicity was nausea/vomiting, which was observed in 55 patients (45%). Phlebitis, which was considered to be caused by dacarbazine, was observed in 22 patients (18%), and three of them used a central venous port system to avoid phlebitis. The toxicities caused treatment discontinuation were observed in 10 patients. Grade 3 pneumonitis induced by bleomycin and *Pneumocystis jirovecii* pneumonia was observed in one patient each. There was no treatment-related death.

Secondary malignancies were observed in 5 patients (4%) during the follow-up

time (median 69 months, range: 6-176 months). Three patients had solid tumors in the field of radiation therapy; one patient had basal cell carcinoma of the skin, one patient had esophageal cancer, and remaining one patient had mycosis fungoides. These tumors occurred approximately 10 years after the initial treatment of HL. One patient who did not receive irradiation in the initial HL treatment suffered breast cancer 3.6 years after chemotherapy. Hematologic malignancy was observed in 1 patient; the patient developed myelodysplastic syndrome one year after the completion of 8 cycles of ABVd.

Cardio-vascular events were observed in 4 patients (3%). One of the 4 patients died of an acute coronary event, which occurred 8 years after thoracic irradiation for mediastinal bulky mass, and one patient had a first-degree atrioventricular block 4 years after thoracic irradiation. The remaining two patients, who had received ABVd without irradiation, had asymptomatic low left ventricular ejection fractions.

Survival

The PFS of 83 early-stage patients and 56 advanced-stage patients are shown in Fig. 1a and their 5-year PFS rates were estimated to be 90% and 71%, respectively. The PFS of advanced-stage patients was significantly worse than that of early-stage patients ($p = 0.014$).

The five-year OS rates of early stage and advanced stage patients were estimated at 94% and 91%, respectively, with no significant difference ($p = 0.95$) (Fig. 1b).

There were 12 deaths: 8 patients with early-stage disease and 4 patients with advanced-stage disease. The causes of death were as follows: disease progression in 4 patients (1 with early-stage disease and 3 with advanced-stage disease), a salvage regimen-related mortality (one patient), allogeneic stem cell transplantation-related mortality (one patient), cardiac event (one patient), secondary malignancy (one patient), double cancer; cancer diagnosed before the initial treatment of HL (one patient) and others (three patients) (Fig. 2).

The results of univariate and multivariate analyses of various factors affecting PFS and OS are shown in Table 4. Among the early-stage patients, no variables were found to be significant adverse factors related to PFS and OS. On the other hand, in the advanced-stage patients, anemia and aged 70 or older were significant adverse factors related to PFS, but not to OS.

## Discussion

Here, we report the treatment outcome of 139 Japanese patients with HL. The present study is the most recent analysis, with the largest number of patients, regarding the detailed treatment outcomes and clinical features of patients with HL in Japan. The OS and

PFS in the present study are as favorable as those of previous prospective clinical trials, even though the present study treatments were performed in a clinical practice setting. In other words, it is likely that the survival of HL patients failed to improve sufficiently compared with those previously reported, despite the development of supportive care in the last decade. Therefore, novel treatment strategies to improve the survival of HL patients are needed.

The main previous reports on HL are shown in Table 5. In these studies, the 5-year survival rate for patients with early-stage HL has consistently been 90% or higher [18-20]. Our study also showed patients with early-stage HL has significantly high survival rate. Therefore, the late onset treatment-related toxicities, such as secondary malignancies and cardiac events, are thought to be a more significantly problematic issue to resolve in early-stage patients.

The German Hodgkin Study Group (GHSG) reported that secondary malignancies occur at an average rate of approximately 1% per year for at least 30 years after treatment [21]. The risk is particularly high among women younger than 30 years of age who receive thoracic radiotherapy; breast cancer develops in 30 to 40% of these patients in the 25 years after treatment [22]. Radiation-related cardiac events are also an important problem. Swerdlow AJ, et al. reported that the risk of death from myocardial infarction is increased

after thoracic radiotherapy, and that the increased risk persists for more than 25 years [23]. In the present study, we experienced 5 secondary malignancies and 4 cardiac toxicities. Although this incidence was lower than that of previous reports, the median follow up duration, only 70 months, was too short to evaluate the actual incidence of these late-onset toxicities. Therefore, further follow-up is needed.

The novel treatment strategy for early-stage HL, aims to reduce the late onset treatment related toxicities. The GHSG reported on a large-scale study that investigated the efficacy of reduced cycles of ABVD with or without reduction in the radiation dose. They concluded that 2 cycles of ABVD followed by 20 Gy of involved-field radiotherapy (IFRT) should be regarded as the standard of care in early favorable HL, with EFS of 91% and OS of 93% at 5 years [20].

On the other hand, advanced-stage HL patients still have a higher relapse rate compared with early-stage disease patients [9, 10, 24]. Several study groups have attempted to improve survival using intensive chemotherapies, such as BEACOPP and Stanford V [25-27]. These regimens may be more effective than ABVD and beneficial for some of the higher risk population; however, the higher rate of toxicities, both acute hematologic toxicities and late toxicities such as secondary malignancies, cardiovascular toxicities and infertility, make us

hesitate to perform these intensive regimens for all advanced-stage patients. Therefore, a method to reasonably select which of the higher risk population may benefit from intensive chemotherapy is needed. In our study, anemia, which is contained in the International Prognostic Score (IPS), was found to be an adverse risk for PFS. Engert A, et al. showed that the advantage of escalated BEACOPP is seen among all IPS subgroups and is not just restricted to the high-risk group; accordingly, the selection of high-risk patients by IPS is not a reliable strategy to discern the subset of patients who may benefit from dose intensification [28]. Recent studies showed that an interim PET scan after 2 cycles of ABVD predicts the prognosis of advanced-stage HL patients more clearly than IPS [29]. Interim PET-based risk-adapted approaches are expected to be useful for distinguishing between patients with a disease that is curable by ABVD and others who need a novel treatment strategy. Phase II trials to assess an interim PET-based response-adapted therapy with dose-escalated BEACOPP are currently ongoing in the United States (SWOG study; S0816, NCT00822120) [30] and in Japan (JCOG-LSG study; JCOG1305, UMIN000019868) [31].

Further refinement of the initial chemotherapeutic regimen combining a novel agent is also expected. Brentuximab vedotin (BV) is an antibody-drug conjugate targeting CD30. It is highly effective for relapsed/refractory HL and a promising treatment option for these

patients recently [32-34]. A phase I study of BV combined with ABVD or AVD for 51 patients with untreated advanced-stage HL was conducted and the CR rate was 96% with manageable toxicity [35]. Based on this study, a global phase III study to compare the clinical outcomes of ABVD with AVD plus BV is currently ongoing (NCT01712490) [36].

The optimal frontline treatment of elderly patients with HL is another important controversial issue. In the present study, the age 70 years or older was an adverse factor related to PFS in the patients with advanced-stage HL. Evans et al also reported the outcome of 95 elderly patients with HL (median age 67, range 60-89) and the age more than 70 years were associated to poor outcome [37]. In these populations, frailty and comorbidity are common and doxorubicin-containing regimens such as ABVD or BEACOPP are inappropriate because of their toxicities. Forero-Torres et al conducted a phase II study to assess the efficacy of brentuximab vedotin monotherapy as a frontline treatment in the elderly patients with HL [38]. Overall response rate was 92% among the 26 evaluable patients with 19 patients (73%) achieving complete remission. Further investigations regarding brentuximab vedotin-containing less toxic regimens as a frontline therapy are expected especially in the elderly patients with HL.

The present study has several limitations. First, this is a single institutional

retrospective study; second, the various potential selection biases associated with this kind of retrospective analysis; third, a fewer number of patients compared with the clinical trials conducted in Western countries. Even so, there is no data available regarding Japanese patients with HL in recent years and the number of patients in this study is larger than other clinical studies previously reported in Japan.

In conclusion, we showed the treatment outcomes of 139 Japanese patients with HL at a single institution. The treatment outcome was as favorable as previously reported, while the patients with advanced-stage disease still have lower PFS compared to the patients with early-stage disease. The present study will provide reference data in future clinical trials for Japanese patients with HL. A further prospective multicenter study is needed to establish a novel treatment strategy and evidence that supports our daily clinical practice on HL.

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**Conflict of interest statement**

None declared.

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TABLES

**FIGURE LEGENDS**

Figure 1. The progression free survival (PFS) (a) and overall survival (OS) (b) of the patients with Hodgkin lymphoma in the present study with a median follow-up duration of 69 months. The estimated 5-year PFS rates for patients with early-stage disease (solid line) and advanced-stage disease (dashed line) were 90% and 71%, respectively. The 5-year OS rates for patients with early-stage disease (solid line) and advanced-stage disease (dashed line) were 94% and 90%, respectively. The PFS of advanced-stage patients was significantly worse than that of early-stage patients ($p = 0.014$), whereas the OS was not ($p = 0.95$).

Figure 2. Causes of death in the present study

Table1 Patient characteristics ( N=139 )

| | | n (%) |
|---|---|---|
| Age | median (years) | 34 |
| | range | 14-83 |
| Gender | male | 83 (60%) |
| | female | 56 (40%) |
| Histology | NS | 79 (57%) |
| | MC | 29 (21%) |
| | LD | 5 (4%) |
| | LR | 3 (2%) |
| | NLPHL | 12 (8%) |
| | Classical HL, NOS | 11 (8%) |
| PS | 0-1 | 135 (97%) |
| | 2 | 3 (2%) |
| | 3 | 1 (1%) |
| Clinical stage | | |
| Early stage | IA | 27 (20%) |
| | IB | 3 (2%) |
| | IIA | 53 (38%) |
| Advanced stage | IIB | 15 (11%) |
| | IIIA | 14 (10%) |
| | IIIB | 3 (2%) |
| | IVA | 14 (10%) |
| | IVB | 10 (7%) |
| Bulky disease | Yes | 31 (22%) |
| | mediastinal | 28 (20%) |
| | non-mediastinal | 3 (2%) |
| International Prognostic Score* (N=56) | | |
| | 0 | 5 (9%) |
| | 1 | 10 (18%) |
| | 2 | 17 (30%) |
| | 3 | 7 (12%) |
| | 4 | 16 (29%) |
| | ≧5 | 1 (2%) |

***NS*** nodular sclerosis; ***MC*** mixed cellularity; ***LD*** lymphocyte depletion; ***LR*** lymphocyte-rich; ***NLPHL*** nodular lymphocyte predominant HL; ***PS*** performance status

*Assessed in 61 advanced disease patients

Table 2 Treatment modalities, regimens and response

| | Modalities | n (%) |
|---|---|---|
| Early-stage | Chemotherapy and RT | 73 (88%) |
| (N=83) | RT alone | 6 (7.2%) |
| | Chemotherapy alone | 4 (4.8%) |
| Advanced-stage | Chemotherapy and RT | 22 (39%) |
| (N=56) | RT alone | 0 |
| | Chemotherapy alone | 34 (61%) |
| | **Regimen of chemotherapy** | **n (%)** |
| Early-stage | ABVd | 74 (96%) |
| (N=77) | (median 6 cycles, range: 2-8 cycles) | |
| | Others | 3 (4%) |
| Advanced-stage | ABVd | 48 (86%) |
| (N=56) | (median 8 cycles, range: 2-8 cycles) | |
| | C-MOPP | 3 (5%) |
| | Others | 5 (9%) |
| | **Response** | **n (%)** |
| Early-stage | CR/CRu | 76 (92%) |
| (N=83) | PR | 4 (5%) |
| Advanced-stage | CR/CRu | 46 (82%) |
| (N=56) | PR | 6 (11%) |

***RT*** radiotherapy; ***CR*** complete remission; ***CRu*** complete remission unconfirmed ; ***PR*** partial remission; ***ABVd*** adriamycin, bleomycin, vinblastine, and dacarbazine; ***C-MOPP*** cyclophosphamide, vincristine, procarbazine,and prednisone

Table 3 Toxicities of ABVd with or without irradiation (N=122)

| | Grade1/2 | Grade 3 | Grade 4 |
|---|---|---|---|
| Adverse event | n (%) | n (%) | n (%) |
| Leukopenia | 108 (89%) | 4 (3%) | 0 |
| Neutropenia | 24 (20%) | 47 (39%) | 40 (33%) |
| Anemia | 107 (88%) | 0 | 0 |
| Thrombocytopenia | 7 (8%) | 0 | 0 |
| Febrile Neutropenia | - | 18 (15%) | 2 (2%) |
| Fever | 12 (10%) | 0 | 0 |
| Nausea/vomitting | 54 (44%) | 1 (1%) | - |
| Phlebitis | 22 (18%) | - | - |

Table 4-1 The risk factors in the 83 early-stage patients

| | | | Univaliate analysis | | | |
|---|---|---|---|---|---|---|
| | | | PFS | | OS | |
| Variable | | n | HR (95%CI) | P value | HR (95%CI) | P value |
| Mediastinal bulky disease | Yes | 17 | .93 (.20-4.3) | .93 | 1.2 (.25-6.2) | .77 |
| | No | 66 | | | | |
| Age | ≧45 | 20 | 2.3 (.71-7.7) | .15 | 1.4 (.32-5.7) | .68 |
| | ＜45 | 63 | | | | |
| LDH | Within normal range | 42 | 2.2 (.67-8.4) | .25 | 1.4 (.26-8.0) | .67 |
| | Without normal range | 41 | | | | |
| B symptoms | Yes | 3 | 3.3 (.42-35) | .26 | 4.3 (.53-35) | .17 |
| | No | 80 | | | | |

***LDH*** lactate dehydrogenase; ***HR*** hazard ratio; ***CI*** confidence interval

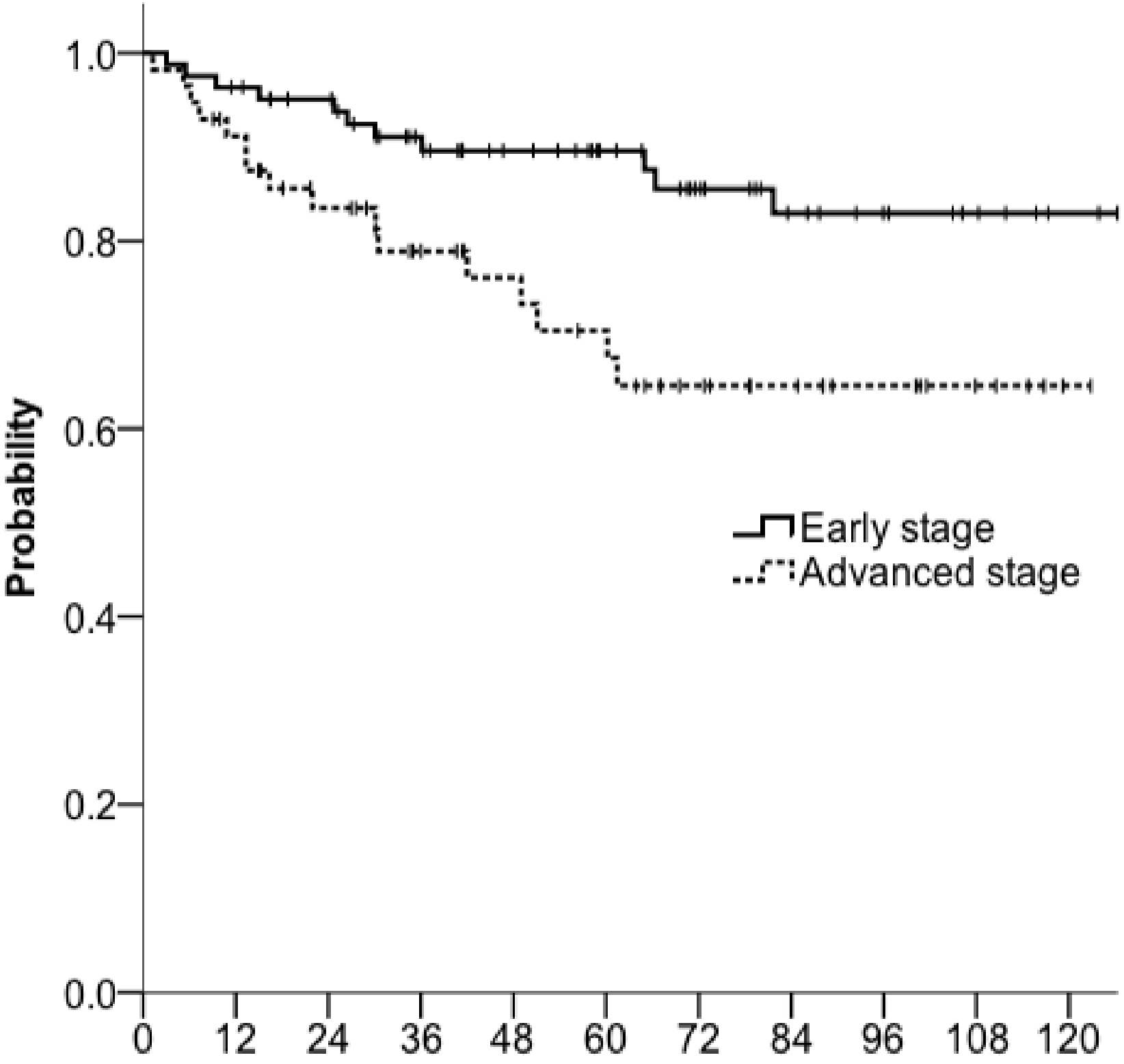
Table 4-2 The risk factors in the 56 advanced-stage patients

| | | | PFS | | | | OS | |
|---|---|---|---|---|---|---|---|---|
| | | | Univariate analysis | | Multivariate analysis | | Univariate analysis | |
| Variable | | n | HR (95% CI) | *P* value | HR (95%CI) | *P* value | HR (95% CI) | *P* value |
| Serum albumin | ＜40 g/L | 31 | 1.9 (.69-5.3) | .21 | — | | 2.9 (.30-28) | .35 |
| | ≧40 g/L | 25 | | | | | | |
| Hemoglobin | ＜105 g/L | 6 | 3.4 (1.1-11) | .032 | 3.6 (1.1-11) | .030 | 2.9 (.31-28) | .35 |
| | ≧105 g/L | 50 | | | | | | |
| LDH | Within normal range | 33 | .86 (.31-2.3) | .76 | — | | .39 (.04-3.8) | .41 |
| | Without normal range | 23 | | | | | | |
| Clinical stage IV | Yes | 24 | 2.1 (.79-5.7) | .13 | — | | 4.9 (.50-47) | .17 |
| | No | 32 | | | | | | |
| Age | ≧70 years | 4 | 6.1 (1.7-22) | .006 | 6.4 (1.7-24) | .005 | 6.3 (.63-64) | .12 |
| | ＜70 years | 52 | | | | | | |
| WBC count | ≧15 x $10^9$/L | 12 | .53 (.12-2.3) | .39 | — | | 1.2 (.13-12) | .86 |
| | ＜15 x $10^9$/L | 44 | | | | | | |
| Lymphocyte count | ＜0.6 x $10^9$/L or ＜8% | 6 | 1.1 (.25-4.9) | .89 | — | | 2.6 (.27-25) | .40 |
| | ≧0.6 x $10^9$/L | 50 | | | | | | |

Table 5 Previous reports of HL

| | Author | Clinical stage | year of recruitment | Treatment | No. of Pts | %CR | %OS (5yr) | %PFS (5yr) |
|---|---|---|---|---|---|---|---|---|
| Early stage | Meyer et al. (JCO 2005, NCIC-CTG) | I-IIA | 1994-2002 | ABVD 4-6 cycles | 196 | NA | 96 | 87 |
| | | | | vs SNRT (35Gy) | 203 | | 94 | 93 |
| | Straus et al. (Blood 2004, MSKCC) | I-IIIA | 1990-2000 | ABVD 6 cycles | 76 | 94 | 90 | 81 |
| | | | | vs ABVD 6cycles + IFRT | 76 | 94 | 97 | 86 |
| | Engert et al. (NEJM 2010, GHSG | Early-stage with low risk | 1998-2003 | ABVD 4 cycles + IFRT 30Gy | 298 | 96 | 97 | 93 |
| | | | | ABVD 4 cycles + IFRT 20Gy | 295 | 97 | 97 | 93 |
| | | | | ABVD 2 cycles + IFRT 30Gy | 295 | 97 | 97 | 91 |
| | | | | ABVD 2 cycles + IFRT 30Gy | 299 | 96 | 97 | 91 |
| | Present study | I-IIA | 1999-2011 | ABVd etc. ± RT | 83 | 91 | 94 | 90 |
| Advanced stage | Duggan et al. (JCO 2003, CALGB and ECOG) | III/IV | - | ABVD | 433 | 76 | 82 | 63 |
| | | | | vs MOPP/ABV | 419 | 80 | 81 | 66 |
| | Diehl et al. (NEJM 2003, GHSG) | IIB-IV | 1993-1998 | dose-escalated BEACOPP | 466 | 96 | 91 | 87 |
| | | | | standard BEACOPP | 469 | 85 | 88 | 76 |
| | | | | COPP/ABVD | 260 | 88 | 83 | 69 |
| | Gobbi et al. (JCO 2005, Italy) | IIB-IV | 1996-2000 | ABVD | 122 | 89 | 90 | 85 |
| | | | | Stanford V | 107 | 76 | 82 | 73 |
| | | | | MOPPEBVCAD | 106 | 94 | 89 | 94 |
| | Viviani et al. (NEJM 2011,Italy ) | IIB-IV | 2003-2007 | ABVD | 168 | 76 | 84 | 73 |
| | | | | BEACOPP | 163 | 81 | 89 | 85 |
| | Takenaka et al. (JJCO 2000, JCOG8905) | II-IV | 1989-1993 | C-MOPP/ABVD | 79 | 84 | 85 | 73 |
| | Ogura et al. (Int J Hematol 2010, JCOG9305) | II-IV | 1993-1997 | ABVd | 128 | 81 | 91 | 78 |
| | Present study | IIB-IV | 1999-2011 | ABVd etc. | 56 | 82 | 91 | 71 |

***NCIC-CTG*** National Cancer Institute of Canada Clinical Trials Group; ***ABVD*** adriamycin, bleomycin, vinblastine, and dacarbazine; ***SNRT*** subtotal nodal radiation therapy; ***MSKCC*** Memorial Sloan Kettering Cancer Center; ***IFRT*** involved-field radiation therapy; ***MOPP*** mechlorethamine, vincristine, procarbazine, and prednisone; ***GHSG*** German Hodgkin Study Group; ***CALGB*** Cancer and Leukemia Group B; ***ECOG*** Eastern Cooperative Oncology Group; ***BEACOPP*** bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; ***COPP*** cyclophosphamide, vincristine, procarbazine, and prednisone; ***MOPPEBVCAD*** mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine; ***C-MOPP*** cyclophosphamide, vincristine, procarbazine, and prednisone.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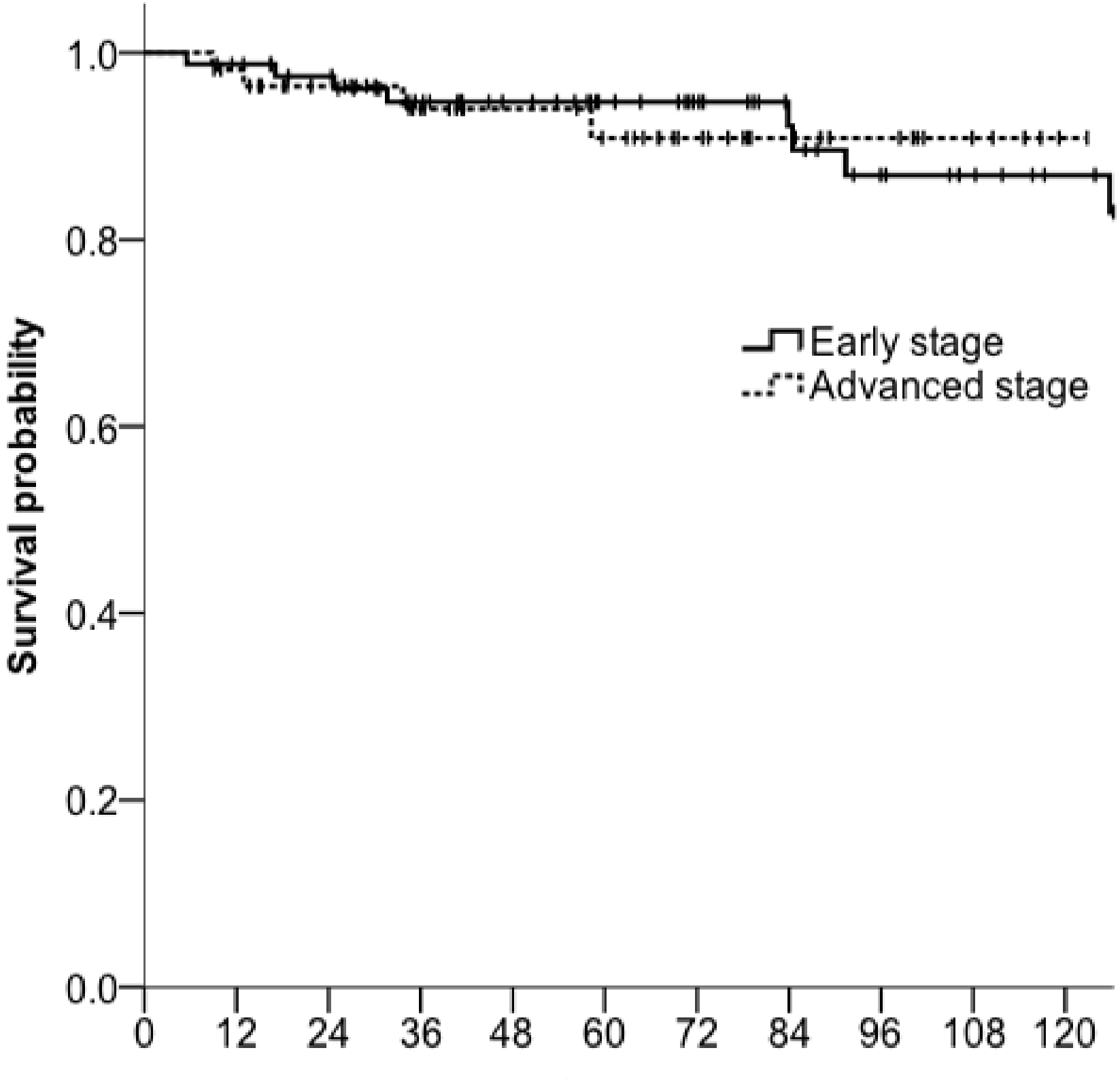
0.6
0.4
0.2
0.0
Probability
0
12
24
36
48
60
72
84
96
108
120
Early stage
Advanced stage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Survival probability
Early stage
Advanced stage
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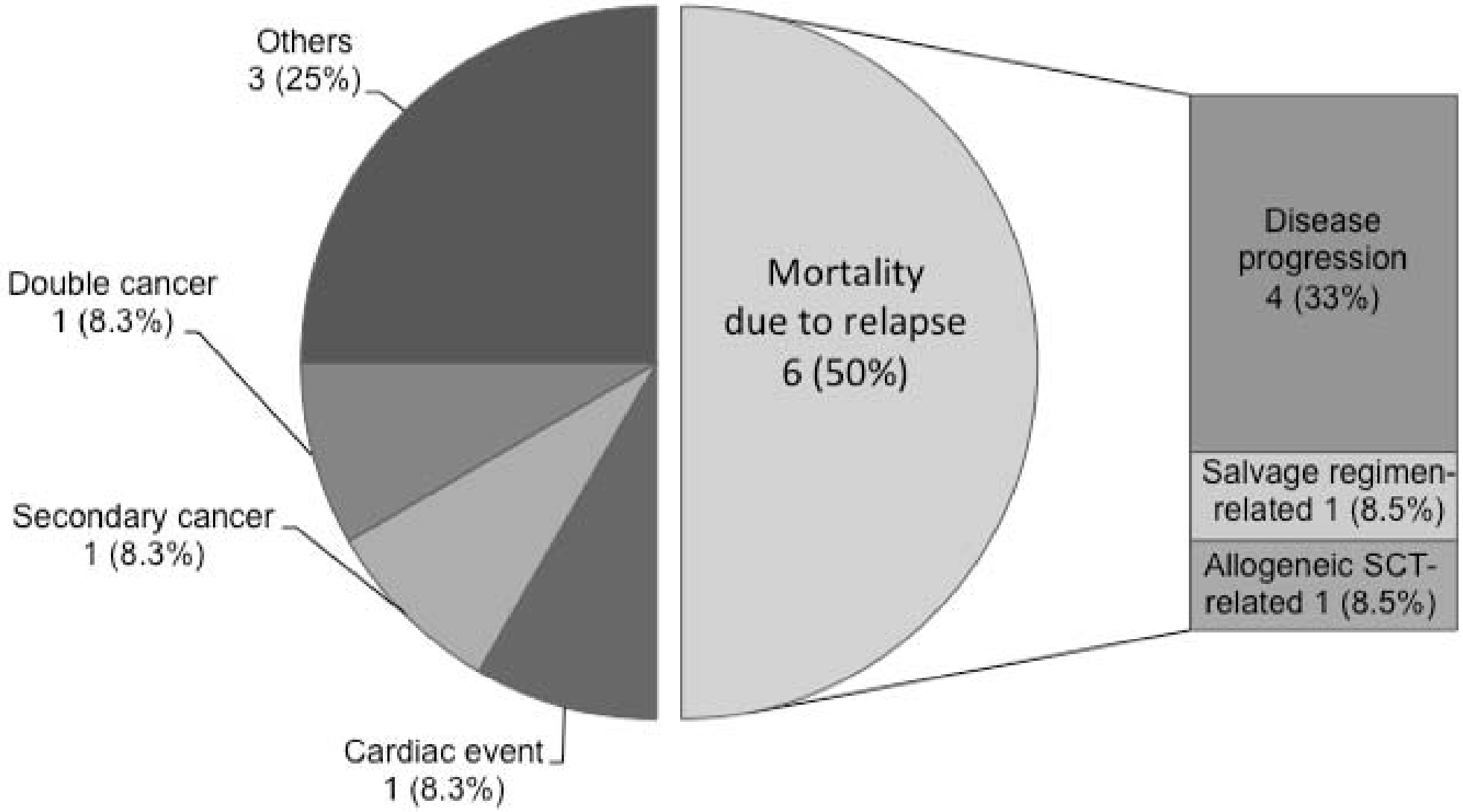
120




| | No. of death | (%) |
|---|---|---|
| All stage (n=139) | 12 | (9%) |
| Early stage (n=83) | 8 | (4.5%) |
| Advanced stage (n=56) | 4 | (4.5%) |