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# Transarterial chemotherapy alone versus transarterial chemoembolization for hepatocellular carcinoma: A randomized phase III trial☆

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***Background/Aims*: Transcatheter arterial chemoembolization (TACE) is a combination of transarterial infusion chemotherapy (TAI) and embolization, and has been widely used to treat patients with hepatocellular carcinoma (HCC). However, since the impact of adding embolization on the survival of patients treated with TAI had never been evaluated in a phase III study, we conducted a multi-center, open-label trial comparing TACE and TAI to assess the effect of adding embolization on survival.**

***Methods*: Patients with newly diagnosed unresectable HCC were randomly assigned to either a TACE group or a TAI group. Zinostatin stimalamer was injected into the hepatic artery, together with gelatin sponge in the TACE group and without gelatin sponge in the TAI group. Treatment was repeated when follow-up computed tomography showed the appearance of new lesions in the liver or re-growth of previously treated tumors.**

***Results*: Seventy-nine patients were assigned to the TACE group, and 82 were assigned to the TAI group. The two groups were comparable with respect to their baseline characteristics. At the time of the analysis, 51 patients in the TACE group and 58 in the TAI group had died. The median overall survival time was 646 days in the TACE group and 679 days in the TAI group ($p = 0.383$).**

***Conclusions*: The results of this study suggest that treatment intensification by adding embolization did not increase survival over TAI with zinostatin stimalamer alone in patients with HCC.**



***Keywords*: Zinostatin stimalamer; Survival benefit; Overall survival; Lipiodol emulsion; Gelatin sponge**

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*Abbreviations:* HCC, hepatocellular carcinoma; AFP, α-fetoprotein; TACE, transarterial chemoembolization; TAI, transarterial infusion chemotherapy; SMANCS, zinostatin stimalamer; CT, computed tomography; TE, therapeutic effect; SMA, styrene maleic acid; NCS, neocarzinostatin.

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## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and a major cause of cancer mortality [1]. Although the screening of populations with a high risk of HCC using ultrasonography and serum α-fetoprotein (AFP) measurements have recently increased the number of candidates for effective local treatments such as hepatic resection and local ablation therapy, many patients exhibit HCCs that are unsuitable for local treatments at the time of the initial diagnosis or at the time of recurrence after local treatment. In these patients, transcatheter arterial chemoembolization (TACE) has been widely used, because TACE induces a marked antitumor effect in HCC.

Several randomized controlled studies have been conducted to assess the survival benefit of TACE compared with conservative therapy [2–9], and an improvement in survival with TACE has been shown in two recent phase III studies [7,8], in both of which TACE was compared with no treatment, and in two meta-analyses [10,11]. However, the impact of adding embolization on the overall survival of patients treated with transarterial infusion chemotherapy (TAI) has never been evaluated in a randomized controlled phase III study. We conducted a multi-centre, open-label trial to compare the effects of TACE and TAI alone to clarify the possible benefits of treatment intensification using embolization in addition to infusion chemotherapy. In this study, zinostatin stimalamer (SMANCS) was selected as the chemotherapeutic agent for use with both TACE and TAI. SMANCS is a lipophilic anti-cancer agent that dissolves in lipiodol to form a stable solution, retaining selectively in HCC. TAI with SMANCS has been widely used in clinical practice to treat patients with advanced HCC in Japan, because it has been reported to have fewer deleterious effects than TACE, especially on liver function, and to have an antitumor effect superior to TAI with other water-soluble agents in non-randomized studies [12,13].

## 2. Methods

Consecutive new patients with HCC were eligible if they had no indications for resection and/or local ablation therapy. The diagnosis was confirmed histologically and/or clinically using angiography and computed tomography (CT). Each patient was required to meet the following criteria: intrahepatic lesions that showed tumor staining by angiography and those in which the total size was less than 50% of the entire liver; adequate hematological function (white blood cells $\geqslant 3000/mm^3$, platelets $\geqslant 50{,}000/mm^3$, and hemoglobin $\geqslant 9.0$ g/dL), adequate hepatic function (serum total bilirubin $\leqslant 2.0$ mg/dL, serum albumin $\geqslant 3.0$ g/dL, serum AST [aspartate aminotransferase] $\leqslant 5$ times the upper limit of normal, serum ALT [alanine aminotransferase] $\leqslant 5$ times the upper limit of normal); adequate renal function (serum creatinine < the upper limit of normal, and serum blood urea nitrogen < the upper limit of normal); an Eastern Cooperative Oncology Group performance status of 0–1; an age of between 20 and 74 years of age; technically eligible for intra-arterial therapy; and written informed consent. Patients were excluded if they met any of the following criteria: a history of allergy to iodine-containing agents and/or contrast material; concomitant malignancy; a history of anti-cancer treatment for HCC; extrahepatic metastasis or tumor thrombus in the portal vein and/or the hepatic vein; intrahepatic arteriovenous shunting; ascites and/or pleural effusion not controlled by diuretics; pregnant or lactating woman and fertile patients not using effective contraception; myocardial infarction within the previous 6 months; or any serious physical and/or mental conditions. The study was performed in accordance with the Declaration of Helsinki, and approved by the ethics committee of each participating center. The study was investigator-designed and investigator-driven, and it received no support from any pharmaceutical companies.

Patients who met the eligibility criteria were provisionally registered before undergoing angiography. After confirmation of technical eligibility and reconfirmation of indications for the protocol intra-arterial treatments in regard to tumor status, including the number of tumors, their vascularity, and vascular invasion based on the angiographic findings, confirmatory registration was completed by each participating investigator. Central randomization to either a TACE group or TAI group was performed by using a telephone randomization system with stratification according to AFP level and treatment center. First, participants were stratified according to AFP level into a group with levels less than 400 ng/mL and a group with levels of 400 ng/mL or more. The group with AFP levels less than 400 ng/mL was further stratified according to treatment center. Randomization was achieved using a computer-generated allocation by permutation of blocks in equal proportions.

The treatments were performed by the participating investigators at 10 Japanese centers. Zinostatin stimalamer (SMANCS; Astellas Pharm Inc., Tokyo, Japan)/lipiodol emulsion (1 mg/mL) was injected slowly under fluoroscopic monitoring into the artery feeding the HCC using a catheter in a superselective manner in both the TACE and the TAI groups. The emulsion was prepared by suspending the SMANCS in lipiodol and shaking just before injection. The volume of the emulsion, up to a maximum of 6 mL (containing 6 mg of SMANCS), was adjusted according to the tumor size and tumor distribution. In the patients in the TACE group, gelatin sponge particles were utilized after the injection of the SMANCS-lipiodol emulsion. Treatment was repeated when a follow-up CT examination showed new lesions in the liver or re-growth of previously treated tumors. Treatment was discontinued if the size of the tumor treated had increased by more than 25% one month after the previous treatment; if there were any vascular contraindications, any exclusion criteria, or any severe adverse effects (defined as grade 4 leucopenia, grade 4 neutropenia, or grade 3 febrile leucopenia/neutropenia, a serum total bilirubin elevation of more than or equal to 5.0 mg/dL, a serum creatinine elevation of more than or equal to 1.5 times the upper normal limit, or grade 3 or greater non-hematological toxicity excluding nausea, vomiting, anorexia, pain, fever, hyperglycemia, fatigue, and serum transaminase elevation), or if the patient so requested.

The primary outcome measure was survival calculated from the date of randomization. Secondary outcome measures were tumor response and toxicity. Antitumor effect was evaluated by CT performed 1 month after the completion of treatment and every 3–4 months thereafter according to the response evaluation criteria proposed by the panel of experts of the Liver Cancer Study Group of Japan [14], which resemble the criteria proposed by the European Association for the Study of the Liver (EASL) Panel of Experts on HCC [15]. Tumor size was measured using the sum of the products of the perpendicular longest diameters of all measurable lesions. In the response evaluation criteria, lipiodol accumulation in the tumors is regarded as an indication of necrosis because significant positive correlations have been reported between lipiodol accumulation observed on CT images and the necrotic regions in resected tumors examined pathologically after TACE and after TAI with SMANCS [13,16,17]. Therapeutic effect V (TE V) is defined as the disappearance or 100% necrosis of all tumors, TE IV as a more than a 50% reduction in tumor size and/or more than 50% necrosis, and TE III as a more than 25% reduction and/or more than 25% necrosis. TE I is defined as a more than 25% increase in tumor size. TE II is defined as disease not qualifying for classification as TE V, IV, III, or I. The serum AFP level of each patient was also measured 1 month after treatment and every 3–4 months thereafter. Toxicity was assessed according to the criteria of the Japan Society for Cancer

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Therapy [18], whose criteria are essentially the same as the WHO criteria [19]. The follow-up period was defined in the protocol as 2 years after the enrollment of the last patient.

### 2.1. Statistical analysis

Based on our previous phase II studies, in which we reported a 2-year survival rate of 80% in patients treated with TACE and of 60% in patients treated with TAI, 70 patients were required in each group to achieve a 90% power to detect superior survival in the TACE group by using a two-sided alpha level of 5% [13,20]. After sensitivity analyses of combinations of survival parameters, we targeted the recruitment of 80 patients in each group. All analyses were conducted based on the intention-to-treatment principle. Survival curves were calculated from the day of randomization using the Kaplan–Meier method and compared using the log-rank test. Comparisons between groups were made using the Wilcoxon test for continuous variables and Fisher's exact test for categorical variables. Analyses were conducted using SAS ver. 8.

## 3. Results

Between October 1999 and June 2003, 222 patients were provisionally enrolled in the study at 10 Japanese centers (Fig 1). Sixty-one of the 222 patients were excluded because of ineligibility for intra-arterial treatment based on the angiographic findings or withdrawal of consent; too few or too many definitive tumors that required reconsideration of the treatment strategy (46), tumor thrombus in the portal vein (3), tumors without sufficient tumor staining (3), intrahepatic arteriovenous shunting (2), allergy to contrast material (1), and withdrawal of consent (6). The most common reason for exclusion was having too few definitive tumors (37/61). The patients who were excluded because of having too few definitive tumors had been considered eligible based on the detection of several small hypervascular nodules on pre-treatment CT imaging that were diagnosed as HCC, but treatment had been switched to local ablation therapy or monitoring based on angiographic findings suggesting that the nodules represented dysplastic nodules. All of the patients who withdrew consent requested TACE for their treatments. The remaining 161 patients were allocated randomly to the TACE group (79 patients) or the TAI group (82 patients). Follow-up was continued through to June 17, 2005, two years after the enrollment of the last patient. Although the baseline data of some eligible patients did not meet the eligibility criteria after they were enrolled, the study protocol permitted initiation of treatment when according to the judgment of the investigator, treatment could be performed safely. Two patients had a pre-treatment serum albumin level that was below the eligibility criterion, but there were no statistically significant differences in baseline characteristics between the two groups (Table 1).

### 3.1. Treatment

The total number of treatment courses was 170 with a mean of 2.2 courses per patient (range, 1–9 courses) in the TACE group and 193 with a mean of 2.4 courses (range, 1–6 courses) in the TAI group. Eight patients in the TACE group and two patients in the TAI group were scheduled for the continuation of protocol treatment as of the date of the last follow-up. The remaining 71 patients in the TACE group and 80 patients in the TAI group had discontinued treatment. The reasons for treatment discontinuation were similar in both groups (Table 2).

### 3.2. Survival

At the time of the final analysis, 51 patients in the TACE group and 58 patients in the TAI group had died. Seven patients in the TACE group and eight in the TAI group were lost to follow-up after the cessation of protocol treatment. The median overall survival time was 646 days in the TACE group and 679 days in the TAI group. The estimated 2-year survival rate was 48.2% for the TACE group and 49.6% for the TAI group. No significant difference in survival was seen between the two groups ($p = 0.383$, Fig. 2).

### 3.3. Antitumor effect

The tumor response on CT was determined in 156 patients (77 in the TACE group and 79 in the TAI group). In the TACE group, there were 8 TE V, 29 TE IV, 31 TE III, 7 TE II, and 2 TE I responses. In the TAI group, there were 5 TE V, 22 TE IV, 30 TE III, 21 TE II, and 1 TE I response. The proportion of patients with TE V or IV among the measurable patients was not significantly different between the TACE group and the TAI group (48.1% vs. 34.2%; $p = 0.11$). There was no significant difference between the two groups in the proportion of patients with a pre-treatment AFP level > 200 ng/mL whose AFP level decreased by more than half (16.5% vs. 13.4%; $p = 0.66$).

### 3.4. Toxicity

Hematological toxicity was relatively mild and transient in both groups, although 2 patients (2.6%) in the TACE group and 3 (3.7%) in the TAI group developed grade 4 thrombocytopenia (Table 3). Major non-hematological toxicities were hyperbilirubinemia, elevations in serum liver enzymes, fever and abdominal pain in both groups. The grade of elevated ALT levels was significantly higher in the TACE group than in the TAI group, although there were no significant differences in any other toxicities between the two groups. No treatment-related death was observed in either group. Two patients in the TACE group and six in the TAI group manifested a grade 1–2 allergic reaction immediately after injection of the SMANCS-lipiodol emulsion. Shivering in the form of trembling of the whole body lasting

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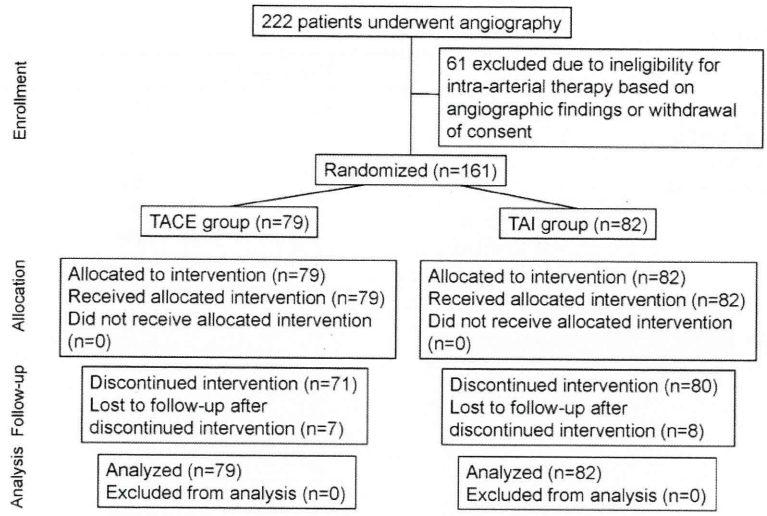


**Fig. 1. Study flow diagram.**

several minutes after the injection was noted in 12 patients in the TACE group and 14 patients in the TAI group, and it was thought to have been caused by SMANCS.

## 4. Discussion

We initiated this randomized study in 1999 because the impact of adding embolization on overall survival

**Table 1**
**Baseline characteristics.**

| No. of patients | | 79 | 82 |
|---|---|---|---|
| Age, year | Median (range) | 65.0 (42–74) | 67.0 (44–74) |
| Gender | Male | 61 (77.2%) | 70 (85.4%) |
| Performance status | 0 | 76 (96.2%) | 77 (93.9%) |
| | 1 | 3 (3.8%) | 5 (6.1%) |
| HBsAg | + | 11 (13.9%) | 7 (8.5%) |
| HCVAb | + | 57 (72.2%) | 60 (73.2%) |
| Alcohol abuse | + | 33 (41.8%) | 28 (34.1%) |
| Albumin, g/dL | Median (range) | 3.6 (2.8–4.6) | 3.6 (3.0–4.6) |
| Total bilirubin, mg/dL | Median (range) | 1.0 (0.4–2.0) | 0.9 (0.3–2.0) |
| AST, IU/L | Median (range) | 63 (16–243) | 69 (18–232) |
| ALT, IU/L | Median (range) | 60 (12–184) | 60 (10–213) |
| Prothrombin time, % | Median (range) | 80 (41–129) | 78.5 (43–111) |
| Platelet count, $\times 10^9$/L | Median (range) | 110 (48–280) | 120 (44–290) |
| | $<100 \times 10^9$/L | 29 (36.7%) | 28 (34.1%) |
| Ascites | + | 3 (3.8%) | 3 (3.7%) |
| Stage* | I | 2 (2.5%) | 4 (4.9%) |
| | II | 18 (22.8%) | 17 (20.7%) |
| | III | 28 (35.4%) | 25 (30.5%) |
| | IV-A | 31 (39.2%) | 36 (43.9%) |
| Tumor distribution | Unilateral | 40 (50.6%) | 36 (43.9%) |
| | Bilateral | 39 (49.4%) | 46 (56.1%) |
| Maximum tumor diameter, mm | Median (range) | 35 (10–330) | 35 (12–350) |
| Number or tumors | 1 | 13 (16.5%) | 11 (13.4%) |
| | 2–5 | 43 (54.4%) | 52 (63.4%) |
| | 6 | 23 (29.1%) | 19 (23.2%) |
| AFP, ng/ml | Median (range) | 68.3 (2.8–79170) | 93.8 (3.1–40,000) |
| | $\geqslant$400 ng/ml | 26 (32.9%) | 27 (32.9%) |
| Serum creatinine, mg/dL | Median (range) | 0.7 (0.4–1.3) | 0.8 (0.5–1.1) |

*Abbreviations:* AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.
Alcohol abuse was defined as ethanol intake $\geqslant$80 g/day for $\geqslant$5 years.
* According to the staging system of the Liver Cancer Study Group of Japan.

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**Table 2**
**Reasons for treatment discontinuation.**

| | TACE group | | TAI group | |
|---|---|---|---|---|
| Ineffectiveness of protocol treatment | 10 | 13% | 10 | 12% |
| Adverse event caused by protocol treatment | | | | |
| Elevation of serum creatinine level | 1 | 1% | 1 | 1% |
| Elevation of alkaline phosphatase level | 2 | 3% | 2 | 2% |
| Dyspnea | 0 | 0% | 1 | 1% |
| Hypotension | 1 | 1% | 1 | 1% |
| Shivers | 0 | 0% | 1 | 1% |
| Abdominal pain | 0 | 0% | 2 | 2% |
| Ascites | 1 | 1% | 0 | 0% |
| Deterioration before subsequent protocol treatment | | | | |
| Extrahepatic metastasis | 4 | 5% | 7 | 9% |
| Portal vein thrombosis | 6 | 8% | 3 | 4% |
| Tumor rupture | 2 | 3% | 0 | 0% |
| Ascites | 9 | 11% | 11 | 13% |
| Liver dysfunction | 9 | 11% | 11 | 13% |
| Poor general condition | 2 | 3% | 2 | 2% |
| Other disease | 1 | 1% | 6 | 7% |
| Technical problem preventing subsequent protocol treatment | 13 | 16% | 9 | 11% |
| Patient's request | 10 | 13% | 11 | 13% |
| Indication for tumor ablation | 1 | 1% | 2 | 2% |
| Protocol treatment ongoing | 7 | 9% | 2 | 2% |
| Total | 79 | | 82 | |

for patients with advanced HCC treated with TAI had not been fully evaluated and because the efficacy of TACE was still being debated at that time in various countries. Moreover, several differences in TACE methods had been noted between clinical practice in East Asian countries, including Japan, and randomized studies conducted in Europe, including differences in the selection of embolization materials, anti-cancer agents and their doses, in treatment intervals, and in patient characteristics such as tumor stage and liver function. In this study, in which our TACE method was introduced, we selected SMANCS as a chemotherapeutic agent for both TACE and TAI. SMANCS is an anti-cancer drug that has been approved by the Japanese government for administration with lipiodol into the artery feeding HCC, and TAI with SMANCS has been widely used instead of TACE in many hospitals because of its favorable antitumor effect and mild toxicity profile.

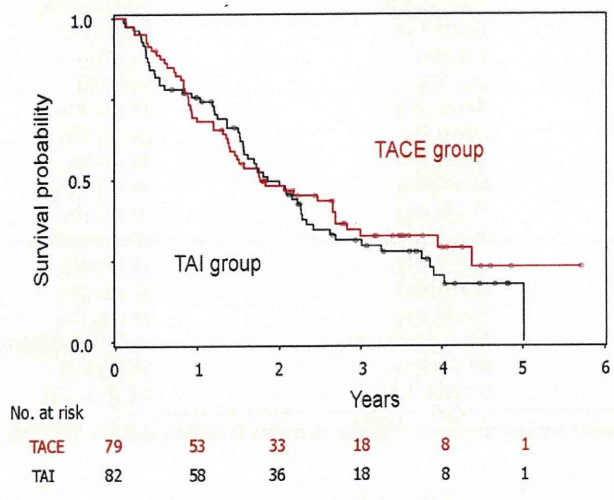


**Fig. 2. Survival curves in the TACE group and in the TAI group.**

This study did not confirm any significant survival advantage of TACE over TAI. A German group also reported that adding transient occlusion using degradable starch microspheres improved neither tumor response nor survival for patients treated with TAI using cisplatin and doxorubicin in a randomized phase II trial [21]. Llovet and Bruix showed that survival benefits were identified with TACE (doxorubicin or cisplatin) but not with embolization alone in their meta-analysis [11]. The survival benefit of TACE can be ascribed to the combination of embolization and chemotherapy.

It could be argued that the absence of a significant difference in survival rates between the TACE group and TAI group in this study is attributable to our methodological strategy for selecting SMANCS as the anti-cancer agent, because the agent may have produced favorable results in the TAI group. SMANCS is a high molecular weight chemical conjugate of a synthetic copolymer of styrene maleic acid (SMA) and the anti-cancer antibiotic protein, neocarzinostatin (NCS) [22,23]. SMANCS is lipophilic and dissolves in lipiodol to form a stable emulsion (SMANCS-lipiodol), which prevents rapid washout of SMANCS into plasma from trapped lipiodol. Furthermore, because of the enhanced permeability of the tumor vasculature and/or poor lym-

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**Table 3**
**Adverse events.**

| | TACE group | | | | | | TAI group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 3 | | Grade 4 | | Grade 1–4 | | Grade 3 | | Grade 4 | | Grade 1–4 | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| *Hematological toxicity* | | | | | | | | | | | | |
| Leukocytes | 1 | 1 | 0 | 0 | 27 | 34 | 0 | 0 | 0 | 0 | 26 | 32 |
| Neutrophils | 1 | 0 | 0 | 0 | 14 | 18 | 0 | 0 | 0 | 0 | 15 | 18 |
| Hemoglobin | 1 | 1 | – | | 25 | 32 | 0 | 0 | – | | 23 | 28 |
| Platelets | 10 | 13 | 2 | 3 | 54 | 68 | 10 | 12 | 3 | 4 | 57 | 70 |
| *Non-hematological toxicity* | | | | | | | | | | | | |
| Total bilirubin | 21 | 27 | 0 | 0 | 60 | 76 | 15 | 18 | 0 | 0 | 62 | 76 |
| Alkaline phosphatase | 2 | 3 | 0 | 0 | 53 | 67 | 2 | 2 | 0 | 0 | 63 | 77 |
| Aspartate aminotransferase | 33 | 42 | 0 | 0 | 77 | 97 | 23 | 28 | 0 | 0 | 79 | 96 |
| Alanine aminotransferase | 28 | 35 | 0 | 0 | 73 | 92 | 16 | 20 | 0 | 0 | 77 | 94 |
| Creatinine | 0 | 0 | 0 | 0 | 13 | 16 | 0 | 0 | 0 | 0 | 16 | 20 |
| Abdominal pain | 0 | 0 | 0 | 0 | 55 | 70 | 2 | 2 | 0 | 0 | 50 | 61 |
| Nausea/vomiting | 1 | 1 | – | | 43 | 54 | 0 | 0 | – | | 39 | 48 |
| Diarrhea | 0 | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 4 | 5 |
| Fever | 2 | 3 | 0 | 0 | 69 | 87 | 1 | 1 | 0 | 0 | 66 | 80 |
| Shivers | 0 | 0 | 0 | 0 | 12 | 15 | 1 | 1 | 0 | 0 | 14 | 17 |
| Allergy | 0 | 0 | 0 | 0 | 2 | 3 | 0 | 0 | 0 | 0 | 6 | 7 |
| Ascites | 1 | 1 | – | | 3 | 4 | 0 | 0 | – | | 0 | 0 |
| Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Hypotension | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 |

A 'dash' (–) indicates the grade was not available.

phatic drainage from the tumor interstitium, macromolecular agents like SMANCS are retained more selectively within tumors [24,25]. In fact, experimental studies have shown that tumor-systemic drug concentration ratios as high as 1000 can be achieved using TAI with SMANCS-lipiodol. Thus, the selective delivery of a long-lasting or slow-release anti-cancer agent may have had a sufficient antitumor effect and survival-prolonging efficacy in the TAI group even if embolization had not been used in combination.

The infrequent protocol treatment repetition in this study is another possible reason for the lack of any difference in survival between the two groups, because the average number of protocol treatments was only 2.2 courses in the TACE group and 2.4 in the TAI group, and thus the maximum anti-cancer potential may not have been achieved. We speculated that the choice of SMANCS was partly responsible for the infrequent repetition because hepatic vascular complications, such as the obstruction of the hepatic artery and the arterio-portal shunt, have been reported as adverse reactions specific to SMANCS [26]. These complications are often followed by liver dysfunction, ascites, and technical problems with regard to subsequent protocol treatment, which were the major reasons for treatment discontinuation in this study. The enrollment of many patients with far-advanced HCC in the present phase III study may have been another reason for the small number of treatment repetitions and the subsequent poor survival: the proportion of patients with a pre-treatment AFP level >200 ng/mL was 40% in the phase III study and 24% in the phase II study. Both the antitumor response and the overall survival of the TACE group were poorer than our expectations: the 2-year survival rate in the TACE group was 48.2% in the present study, as opposed to 79% in the phase II study of TACE with SMANCS.

In conclusion, the results of this study suggest that treatment intensification by adding embolization did not increase the survival of HCC patients over SMANCS transarterial chemotherapy alone. The results of this study also showed no significant differences in toxicity, except for an ALP elevation, between the two groups treated with SMANCS. It should be emphasized that the negative results in this study may be attributable to our methodological strategy for selecting SMANCS and the enrollment of many patients with far-advanced HCC. The infrequent treatment repetition and the favorable results of TAI with SMANCS are speculated to be reasons for the lack of any difference in survival between the two groups. Furthermore, the results of this study must be interpreted with caution because current TACE protocols have evolved thanks to the implementation of updated devices including new embolic agents and improved catheters. Additional studies will be required to determine whether the results obtained in this trial are consistent with the results of transarterial treatment with chemotherapeutic agents other than SMANCS and with updated procedures, although it would be difficult to conduct such studies because many consider TACE to be the standard treatment based on the positive results obtained in two recent randomized studies in which doxorubicin or cisplatin was used

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[7,8]. There is a more pressing need for the establishment of new and more active treatment strategies that are superior to conventional TACE to improve the dismal prognosis of this disease.

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ORIGINAL ARTICLE

# Prognostic analysis and a new risk model for Hodgkin lymphoma in Japan

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**Abstract** The Japan Clinical Oncology Group conducted two multicenter phase II trials in 200 patients with advanced Hodgkin lymphoma (HL) in the 1990s. Among 181 patients whose histopathological specimens were available and reviewed by 6 hematopathologists, 167 (92.3%) were diagnosed with HL. Five-year overall survival (OS) among these 167 patients was 88.3%, including 89.2% among nodular sclerosis and 82.2% among mixed cellularity cases. International prognostic score was not closely associated with OS. Seven unfavorable prognostic factors for OS on univariate analysis were male, B symptoms, clinical stage of III

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or IV, elevated serum LDH, elevated alkaline phosphatase, elevated $\beta$2-microglobulin, and pathological subtype (mixed cellularity and lymphocyte depletion). On multivariate analysis, male [HR 3.30 (95% CI 1.15–9.52, $p = 0.027$)] and elevated serum LDH [HR 2.41 (95% CI 1.07–5.43, $p = 0.034$)] were independent factors for OS. Based on these prognostic factors, the 5-year OS was 95.7% in the low-risk group (no adverse factor), 87.9% in the intermediate-risk group (1 adverse factor) and 73.3% in the high-risk group (2 adverse factors). This simple prognostic model for HL warrants further validation studies.

**Keywords** International prognostic score · Multicenter phase II trial · Prognostic factor · Overall survival · Male gender · LDH

## 1 Introduction

Most of the patients with advanced Hodgkin lymphoma (HL) could be induced into complete remission (CR) with state-of-the-art combination chemotherapy or chemo-radiotherapy, and in patients with advanced HL who relapsed after achieving CR, there are some therapeutic options for curing the disease, including conventional salvage chemotherapy and high-dose chemotherapy followed by autologous stem-cell transplantation [1]. However, the excellent outcomes in the initial treatments for HL do not necessarily result in excellent survival, because 20–30% of patients with advanced HL are not cured of their disease, and moreover, the treatments are associated with increased risks of late toxicities such as secondary malignancies, cardiopulmonary toxicities, and cerebrovascular diseases [2–5]. It still seems to be necessary to identify the high-risk group of the minority of patients with fatal outcome.

Many prognostic factors for failure-free survival have been described in patients with advanced HL. These included age, sex, clinical stage, B symptoms, number of nodal sites, laboratory data such as serum albumin, hemoglobin, white cell count, lymphocyte count, etc. [6]. The international prognostic score (IPS) [7] was widely accepted as the prognostic index in advanced HL. However, only 7% of the patients had the worst adverse score of 5 or higher of IPS which represents a very high risk, and was associated with 56% of the overall survival (OS) at 5 years. Thus, it was concluded that a distinct group of patients at very high risk could not be identified by the IPS [7].

Considering the various effective treatment options and their late toxicities, it is important to identify the prognostic factors for OS in patients with advanced HL. In particular, this is relevant to the question of whether early high-dose chemotherapy with autologous stem-cell transplantation should be used as a consolidation therapy in patients with responses to induction therapy, who are nevertheless considered to remain at high risk for relapse. To address the ability to predict the prognosis of patients with advanced HL, we analyzed patients with advanced HL enrolled in the Japan Clinical Oncology Group-Lymphoma Study Group (JCOG–LSG) trials. The aims of this study were to validate the IPS in terms of OS, to evaluate the OS according to several prognostic factors including histological subtypes of HL, and to find a better prognostic model for patients with advanced HL, who were enrolled in JCOG–LSG trials with state-of-the-art combination chemotherapy or chemo-radiotherapy.

## 2 Patients and methods

### 2.1 Patients and treatments

The JCOG–LSG conducted two multicenter phase II trials for advanced HL in the 1990s that tested the efficacy of the ABVd regimen (JCOG9305) [8] and ABV regimen followed by involved-field radiotherapy (IF-RT) (JCOG9705) [9]. Major eligibility criteria were age between 15 and 69 years, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 in the two trials, and clinical stage of II, III or IV in JCOG9305 and clinical stage of IB, IIB, III, or IV or any stage with bulky lesion in JCOG9705. Bulky lesion was defined as a mass of at least 10 cm (largest diameter) and a bulky mediastinum (ratio of the mediastinum to the thorax of at least one-third at the level of the largest diameter while the patient was standing). A total of 128 patients from 35 participating institutes were enrolled in JCOG9305 between 1993 and 1997 to assess the efficacy of the ABVd regimen, which consisted of doxorubicin, bleomycin, vinblastine and a reduced dose of dacarbazine of two-thirds (250 mg/m$^2$) of that in the original ABVD regimen. The reasons for modification of

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the original ABVD regimen in both JCOG studies were that dacarbazine was highly emetic and it was not approved for the treatment of HL in Japan at that time. In JCOG9705, a total of 72 patients from 25 participating institutes were enrolled between 1998 and 2000 to assess the efficacy of the ABV regimen, in which the dose of doxorubicin was increased to 120% of that in the original ABVD regimen and dacarbazine was not utilized. Patients were evaluated for response after 4 cycles of chemotherapy. All patients received 2 additional cycles of chemotherapy. For those with CR after 4 cycles, chemotherapy was finished after a total of 6 cycles. Patients who were in CR or uncertain CR (CRu) after 6 cycles were given 2 additional cycles of chemotherapy. In patients with bulky lesions, IF-RT with 30–40 Gy was added if patients entered into CR or CRu after 4 or 6 cycles. Regardless of whether the lesion was bulky or non-bulky, IF-RT was added if patients entered into partial remission (PR) in JCOG9705.

CR was defined as the disappearance of all measurable or assessable diseases and all signs and symptoms of the disease lasting for at least 4 weeks. PR was defined as a reduction of 50% or greater in the sum of the perpendicular diameters of all measurable lesions and the appearance of no new lesions for at least 4 weeks. CRu was defined as the maintenance of PR for at least 3 months without any treatment. Progressive disease was defined as an increase of 25% in the size of any lesion or development of any new lesions. Relapse was defined as an increase of 25% in the size of any lesion or development of any new lesions in CR or CRu patients. The details of the results of each clinical study will be published elsewhere.

All of the protocols described above including the informed consent document were approved by both the JCOG Protocol Review Committee and the institutional review board of each institution. The protocol of JCOG0108A, an ancillary study with secondary use of the data acquired by the above-mentioned JCOG studies, was also approved by the JCOG Protocol Review Committee.

### 2.2 Consensus diagnosis

The procedure of reaching a consensus diagnosis of HL according to the WHO classification has been described [10]. Briefly, 6 hematopathologists consisting of 4 panelist pathologists and 2 consulting pathologists reviewed the histopathological specimens independently. Immunohistochemical studies were conducted on paraffin sections by means of the avidin–biotin–peroxidase complex technique and a panel of monoclonal antibodies including antibodies against CD20 (L26; DakoCytomation, Glostrup, Denmark), CD3 (PS-1; Novocastra, Newcastle, UK), CD15 (MMA; Becton Dickinson, San Jose, CA, USA) and CD30 (BerH2; DakoCytomation, Glostrup, Denmark). All 6 hematopathologists and 1 hematologist performed the central pathologic review, in which the case report forms of the patients were available for reference of clinical information. A consensus diagnosis was established when agreement was reached by three-fourths or greater majority of the 4 panelist pathologists with no opposition from the 2 consulting pathologists and the hematologist. The cases with discordant pathological diagnosis were re-evaluated until agreement by two-thirds or greater majority was reached among the 6 pathologists by means of reconciliation. Then, a consensus diagnosis was made. The present study included patients in two multicenter phase II trials for advanced HL who were diagnosed with HL by central pathological review.

### 2.3 Statistical analysis

All statistical analyses were performed by a statistician (K.Y.) at the JCOG Data Center. Patients with lymphocyte depletion had been reported as having a worse prognosis than those with other subtypes [11], but this subgroup contained only 7 patients in this study. Therefore, patients with lymphocyte depletion were grouped together with patients with mixed cellularity who had also been shown to have a worse prognosis [12]. OS was the endpoint of all statistical analyses. OS was calculated from the date of enrollment in respective study to the date of death from any cause or to the date of last follow-up in living patients. OS was estimated by the Kaplan–Meier method. The log-rank test was used to assess the significance of unadjusted differences in OS for each prognostic factor. Multivariate analysis was performed by the Cox proportional hazards model to identify subsets of prognostic factors for OS. All $p$ values were two-sided and $p$ values less than 0.05 were considered significant. There is no widely agreed approach to building a multivariate prognostic model from a set of candidate predictors [13, 14] and, in consideration of the limitation of events in our study, the data were analyzed from points of significancy and parsimony. A prognostic model was established by fitting all variables that significantly influenced OS in multivariate analysis, and the risk groups were identified according to the established model. For comparing OS between the risk groups, the overfitting-corrected $p$ values were derived by fivefold cross-validation. All statistical analyses were performed using SAS release 9.1.3 (SAS Institute, Inc., Cary, NC).

## 3 Results

### 3.1 Histopathological distribution

Among the 200 patients from 41 participating institutes in Japan who were enrolled in two multicenter phase II trials

**Table 1** Histopathological distribution of advanced HL among 167 patients

| | Number of patients (%) |
|---|---|
| Nodular lymphocytic predominance | 2 (1.2) |
| Nodular sclerosis | 115 (68.9) |
| Lymphocyte-rich | 3 (1.8) |
| Mixed cellularity | 34 (20.4) |
| Lymphocyte depletion | 7 (4.2) |
| Unclassifiable | 6 (3.6) |

for advanced HL (128 in JCOG9305 and 72 in JCOG9705), histopathological specimens from 181 patients were available and reviewed, and a consensus diagnosis of HL was reached in 167 (92.3%) (107 in JCOG9305 and 60 in JCOG9705) according to the WHO classification. The remaining 14 patients were diagnosed with diffuse large B cell lymphoma ($n = 4$), T cell-rich B cell lymphoma ($n = 4$), anaplastic large cell lymphoma ($n = 1$), angioimmunoblastic T cell lymphoma ($n = 1$) or other ($n = 4$). The histopathological distribution of the 167 patients with HL is shown in Table 1. Among the HLs, nodular sclerosis ($n = 115$) comprised 68.9% of the whole HL and mixed cellularity ($n = 34$; 20.4%) was the next most frequent subtype in Japan.

### 3.2 Clinical characteristics

Data from these 167 patients with HL were analyzed. Their clinical characteristics are shown in Table 2. The median age of the patients at diagnosis was 31 years (range 15–69 years). There was a slight male predominance with males comprising 55%. Seventy-six patients (45%) had B symptoms and 49 patients (29%) had extranodal sites.

### 3.3 OS according to histology and IPS

The 5-year OS of the 167 patients was 88.3% (Fig. 1) (92.3% in JCOG9305 and 81.3% in JCOG9705). The median OS of patients with mixed cellularity was 7.5 years, and those of patients with other histological subtypes was longer than 7.5 years. The 5-year OS of patients with the main histological subtypes was 89.2% in nodular sclerosis and 82.2% in mixed cellularity. The 5-year OS among patients with IPS score of 0, 1, 2, 3, 4, or 5 + 6 was 100% (15 patients), 95.5% (47), 87.5% (40), 86.1% (38), 76.6% (22), or 60.0% (5), respectively (Fig. 2a). Therefore, we failed to identify very high-risk patients by IPS in our study. The OS among patients according to IPS score of 0–2 or 3 and higher is shown in

**Table 2** Patient characteristics ($n = 167$)

| | Number of patients (%) |
|---|---|
| Sex | |
| Male | 92 (55.1) |
| Female | 75 (44.9) |
| Age (years) | |
| ≥45 | 45 (26.9) |
| <45 | 122 (73.1) |
| Performance status (0/1/2/3) | 108/49/7/1 |
| B symptoms | |
| Yes | 76 (45.5) |
| No | 89 (53.3) |
| Clinical stage | |
| I/II | 83 (49.7) |
| III | 49 (29.3) |
| IV | 35 (21.0) |
| Bulky mass | |
| Present | 45 (26.9) |
| Absent | 121 (72.5) |
| Extranodal sites (0/1/≥2) | 106/35/14 |
| Sites of organ involvement | |
| Liver (yes) | 11 (6.6) |
| Lung (yes) | 16 (9.6) |
| Bone marrow (yes) | 10 (6.0) |
| Other (yes) | 29 (17.4) |
| Baseline hematological data | |
| Hemoglobin (<10.5 g/dl) | 28 (16.8) |
| White blood cells (≥15000/μl) | 25 (15.0) |
| Lymphocytes (<600/μl or <8%) | 32 (19.2) |
| Platelets (<100000/μl) | 1 (0.6) |
| Albumin | |
| <4 g/dl | 99 (59.3) |
| ≥4 g/dl | 68 (40.7) |
| Serum LDH | |
| Elevated | 56 (33.5) |
| Normal | 110 (65.9) |
| Alkaline phosphatase | |
| Elevated | 74 (44.3) |
| Normal | 92 (55.1) |
| CRP | |
| Elevated | 128 (76.6) |
| Normal | 29 (17.4) |
| β2-Microglobulin | |
| >2 mg/l | 39 (23.3) |
| ≤2 mg/l | 72 (43.1) |

Data on performance status, B symptoms, bulky mass, extranodal sites, serum LDH, alkaline phosphatase, CRP or β2-microglobulin were missing in 2, 2, 1, 12, 1, 1, 10 or 56 patients, respectively

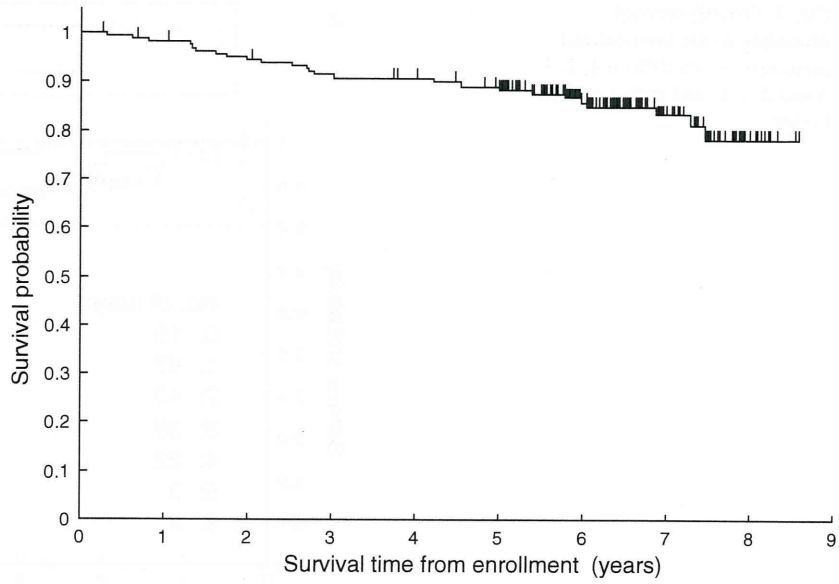


**Fig. 1** Kaplan–Meier curves for overall survival among all patients with HL ($n = 167$)

Fig. 2b. An IPS score of 3 or greater was not a significant unfavorable prognostic factor for OS [HR 2.39 (95% CI 1.10–5.21, $p = 0.03$) by univariate analysis and HR 1.20 (95% CI 0.50–2.89, $p = 0.68$) by multivariate analysis with adjustment of other covariates, which were significant in univariate analysis] and thus, IPS was not closely associated with OS. Therefore, we attempted to identify the prognostic factors for OS in Japanese patients with advanced HL by central pathological review.

### 3.4 Unfavorable prognostic factors by multivariate analysis

Seven unfavorable prognostic factors for OS identified by univariate analysis were male, elevated $\beta$2-microglobulin, B symptoms, elevated serum LDH, elevated alkaline phosphatase, clinical stage of III or IV and pathological subtype (mixed cellularity and lymphocyte depletion) (Table 3). Although data of $\beta$2-microglobulin were available in only 111 patients (66%), we performed multivariate analysis including $\beta$2-microglobulin, but no significant factor was detected. Then, the $\beta$2-microglobulin level was excluded from the final multivariate analysis. Male [HR 3.30 (95% CI 1.15–9.52, $p = 0.027$)] and elevated serum LDH [HR 2.41 (95% CI 1.07–5.43, $p = 0.034$)] were significant unfavorable prognostic factors for OS on multivariate analysis (Table 4). Besides, male and elevated serum LDH remained significant in the multivariate analysis including albumin (data not shown). Similarly, elevated serum LDH remained significant in the multivariate analysis including IPS (each 6 categories and 0–2 or 3–6) after sex was excluded (data not shown).

The OS by sex and serum LDH among patients with HL excluding those with unclassifiable histopathology is shown in Fig. 3a and b, respectively. The 5-year OS was 82.4% in males and 94.4% in females, and 82.4% in patients with elevated serum LDH and 90.5% in patients with normal serum LDH.

### 3.5 Risk group model

The two important prognostic factors identified by the multivariate analysis, i.e., male and elevated serum LDH, were combined in a prognostic index to create risk groups with possible values of 0, 1 and 2 in order of worsening prognosis. Hazard ratios of the final model were as follows: male [HR 4.91 (95% CI 1.84–13.13, $p = 0.002$)] and elevated serum LDH [HR 2.72 (95% CI 1.25–5.89, $p = 0.01$)]. The 5-year OS among patients with HL excluding those with unclassified histopathology was 95.2% in the low-risk group (no adverse factor, $n = 47$), 87.9% in the intermediate-risk group (1 adverse factor, $n = 86$) and 73.3% in the high-risk group (2 adverse factors, $n = 27$). Data on serum LDH were missing in 1 patient. The OS curves of the 3 risk groups are shown in Fig. 4 (corrected $p = 0.004$ by fivefold cross-validation).

## 4 Discussion

It is recognized that there is an uneven geographical distribution of malignant lymphomas throughout the world. Namely, the incidence of T cell lymphoma is relatively high in Asia compared with Western countries. On the contrary, the incidence of HL in Japan was reported to be 4.4% of malignant lymphomas and this is relatively low compared with those in Western countries [11, 15, 16]. The low incidence of HL in Japan limited the evaluation of the

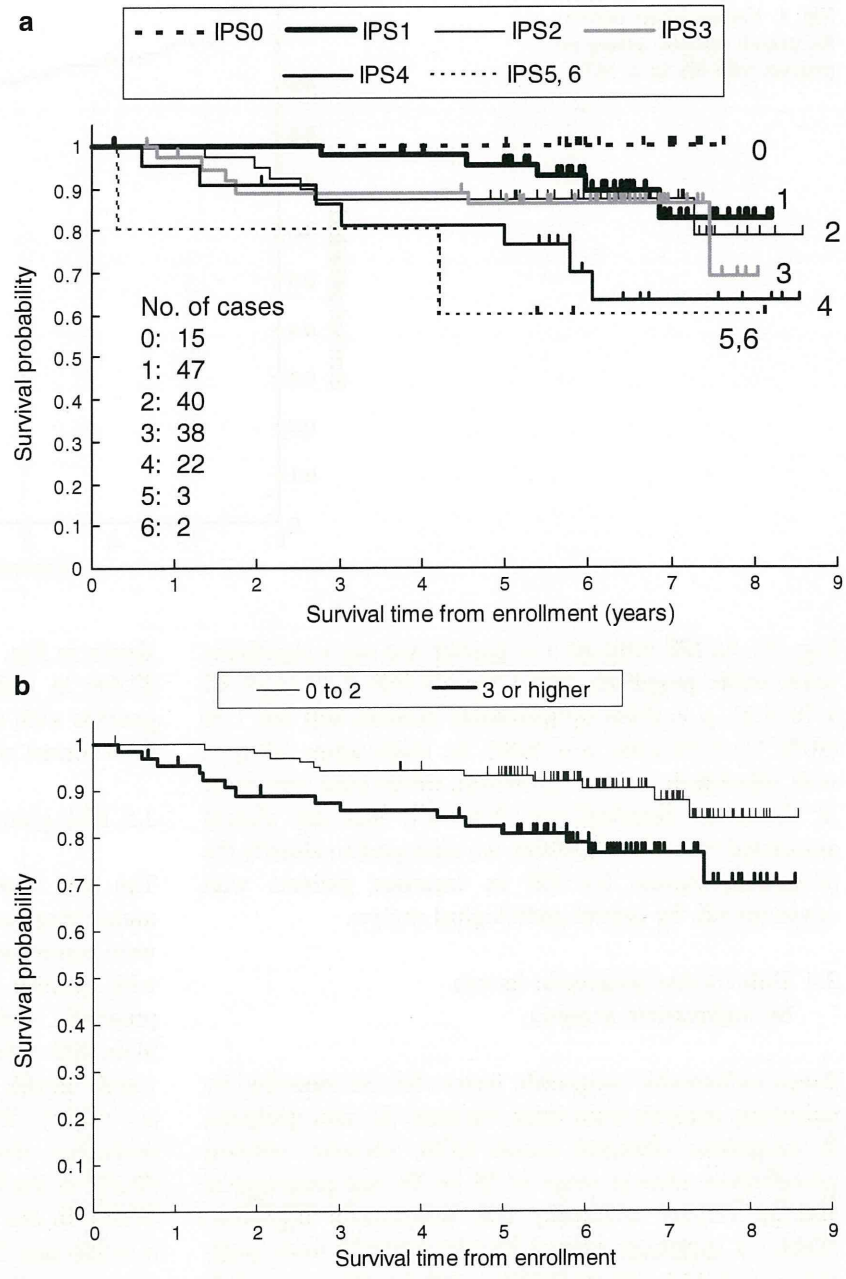


**Fig. 2** Overall survival according to the international prognostic score (IPS) **a** 1, 2, 3, 4 and 5 + 6, and **b** 0–2 or 3 or higher

applicability of IPS or other prognostic factors to Japanese patients with advanced HL treated with an established protocol considered to be state-of-the-art combination chemotherapy or chemo-radiotherapy. To our knowledge, this is the first report to validate the IPS comprehensively and to analyze the conventional prognostic factors for OS in a large number of Japanese patients with advanced HL treated with established protocols of state-of-the-art combination chemotherapy or chemo-radiotherapy and diagnosed by central pathological review. The histopathological distributions of advanced HL according to the WHO classification in 167 patients in Japan were determined, and showed that the proportion of patients with nodular sclerosis in Japan (68.9%) was higher, while the proportion with mixed cellularity (20%) was similar to those in Western countries [12, 16]. The survival of each HL subtype in Japan was similar to those in Western countries [12].

In our study, there were only 5 patients with IPS score of 5 or higher, accounting for only 3% of the entire study population. Their 6-year OS was 60%, indicating that a distinct group of patients at very high risk could not be determined on the basis of IPS. Even in the original IPS paper, only 7% of the patients had a score of 5 or higher representing a very high risk and had a 59% of OS at 5 years. The results were very similar to our study.

**Table 3** Univariate survival analysis

| | | Hazard ratio | 95% CI | *p* |
|---|---|---|---|---|
| Sex | Male | 4.30 | (1.62–11.45) | 0.004 |
| β2-Microglobulin | >2 mg/l | 4.78 | (1.49–15.27) | 0.008 |
| B symptoms | Yes | 0.31 | (0.13–0.74) | 0.009 |
| Serum LDH | Elevated | 2.55 | (1.18–5.51) | 0.02 |
| Alkaline phosphatase | Elevated | 2.53 | (1.13–5.67) | 0.03 |
| Clinical stage | III/IV | 2.41 | (1.05–5.56) | 0.04 |
| Histopathology | MC&LD | 2.21 | (1.02–4.83) | 0.05 |
| Albumin | <4 g/dl | 2.44 | (0.98–6.09) | 0.06 |
| Age (years) | ≥45 | 1.80 | (0.82–3.96) | 0.15 |
| Hemoglobin | <10.5 g/dl | 0.36 | (0.08–1.51) | 0.16 |
| White blood cells | ≥15000/μl | 1.83 | (0.73–4.55) | 0.20 |
| Lymphocytes | <600/μl or <8% | 1.63 | (0.69–3.88) | 0.27 |
| Clinical stage | IV | 1.40 | (0.59–3.32) | 0.45 |
| Extranodal sites | Yes | 0.97 | (0.40–2.39) | 0.95 |

**Table 4** Multivariate survival analysis

| | | Hazard ratio | 95% CI | *p* |
|---|---|---|---|---|
| Sex | Male | 3.30 | (1.15–9.52) | 0.03 |
| Serum LDH | Elevated | 2.41 | (1.07–5.43) | 0.03 |
| B symptoms | Yes | 2.26 | (0.85–6.06) | 0.10 |
| Alkaline phosphatase | Elevated | 1.94 | (0.70–5.37) | 0.21 |
| Histopathology | MC&LD | 1.73 | (0.75–4.00) | 0.20 |
| Clinical stage | III/IV | 0.87 | (0.31–2.47) | 0.80 |

Therefore, in our study, it can be concluded that a distinct group of patients at a very high risk could not be identified by IPS, as same as stated in the original IPS paper [7]. Furthermore, the survival curves of patients with an IPS score of 1, 2 or 3 were not clearly separated from each other (Fig. 2). Therefore, IPS was not closely associated with OS in our study. It has been reported that the IPS score 0–4 versus 5 or 6 was found to have prognostic significance for disease-specific survival in a report of large number of Japanese patients with HL treated variously, in which the presence of T cell and/or cytotoxic antigen in Hodgkin's and Reed-Sternberg cells also showed a significant poor prognosis [17]. However, in that study, neither patient number nor survival rate of patients in each IPS score was shown at all, thus it may be said that IPS was not adequately validated in Japanese patients with advanced HL treated with state-of-the-art combination chemotherapy or chemo-radiotherapy. As it had been concluded that a distinct group of patients at very high risk could not be identified by the IPS [7], attempts have been made to determine more suitable factors that could detect the poor-risk population among patients with HL [17–19]. Namely, it was reported that the number of involved anatomic sites combined with the IPS [18] or interleukin-10 (IL-10) level added to the IPS [19] could detect the subgroup of HL patients with poor prognosis.

As the initial treatments for HL led to excellent outcomes and the rescue treatments could improve the clinical outcomes, the prognostic factors for OS might be more important than the prognostic factors for progression-free survival (PFS) in patients with advanced HL. In our study in which the diagnosis of HL was based on central pathological review, OS was independently affected by male and elevated serum LDH on multivariate analysis. Only male and clinical stage of III or IV among the 7 factors in the IPS were significantly associated with poor OS in the univariate analysis, and male remained significant in the multivariate analysis. The German Hodgkin Study Group suggested that hematotoxicities were more pronounced in females although this did not translate into increased infection, and female patients had similar response rates as males but fewer relapses and deaths, leading to a significantly better freedom from treatment failure in a large retrospective analysis [20]. Sex might be associated with the metabolism of anticancer drugs [21]. Elevated serum LDH was previously reported to be prognostically unfavorable in advanced HL [22, 23] and is also one of the most important factors in the international prognostic index of non-HL [24]. Therefore, elevated serum LDH might reflect the total status of HL, including both constitutional and disease-related elements.

As a post hoc sensitivity analysis, we also performed the analysis using stepwise variable selection methods, and the results were shown that male [HR 6.18 (95% CI 2.28–16.70, $p < 0.001$)] and elevated serum LDH [HR 2.87 (95% CI 1.32–6.24, $p = 0.008$)] remained significant and serum albumin level of less than 4 g/dl [HR 3.38 (95% CI 1.35–8.51, $p = 0.01$)] was also significant. Although serum albumin was significantly correlated with B symptom ($p < 0.001$) and serum alkaline phosphatase ($p = 0.001$), serum albumin did not show the significancy over male and serum LDH as the prognostic factor and did not show the prognostic relevance for OS in univariate analyses. Although stepwise variable selection method was widely used, model by stepwise method is not necessarily considered the best with regard to the statistical issues, which were often discussed and criticized [25–28]. In this study, analysis was performed following the prospectively planned method, and the final model was evaluated by cross-validation, one of the internal validation methods to resolve these statistical issues. The OS curves between risk groups derived from our final model were significantly different, and the results were validated by cross-validation. Based

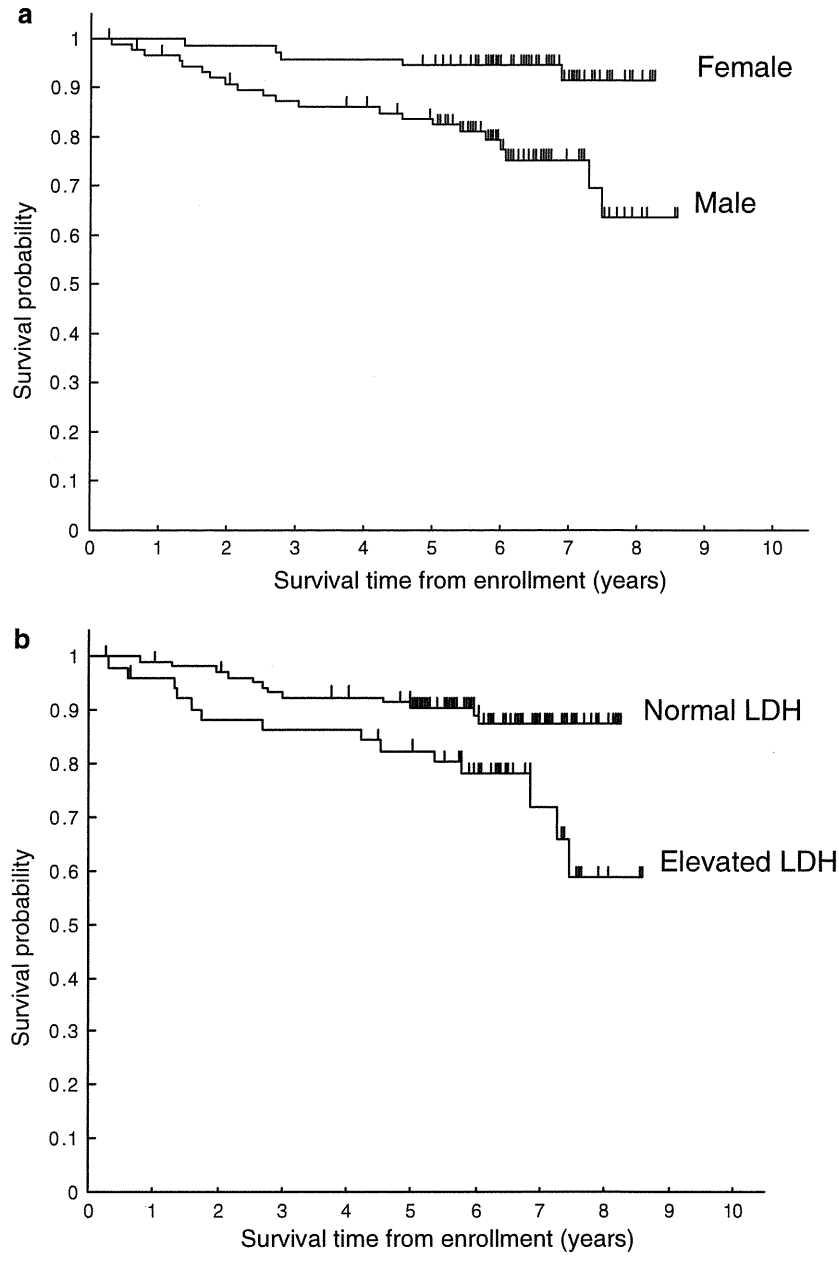


**Fig. 3** Overall survival according to **a** sex ($n = 167$) and **b** serum LDH ($n = 166$)

on a combination of model fit and parsimony considerations, our final model incorporated two prognostic factors: male and elevated serum LDH.

Generally, complex models with a large number of prognostic predictors are not practical and simple models are easier to evaluate and are preferable in routine clinical practice. The prognostic model for advanced HL in our study, including sex and serum LDH, was considered to be very simple. However, it is discussed that prognostication with the prospective studies has a limitation by the exclusion of patients with poor condition and prognostic models using data of prospective study might be difficult for generalization. On this concern, adequate consideration should be necessary.

Prognosis of the patients with advanced HL is improved in advance of treatment, and then prognostic factors may differ according to the state of the treatment. In the original IPS paper, eligible patients with advanced HL for the original IPS study were limited to those who were 15–65 years old and were treated with an established protocol still considered to be state-of-the-art, with at least four planned cycles of combination chemotherapy (preferably containing doxorubicin) with or without radiotherapy. This means that IPS was established in the patients who could be safely treated with state-of-the-art therapy, excluding both elderly patients of more than 65 years and those who were poorly treated probably because of poor condition. Nonetheless, IPS has been used widely, because

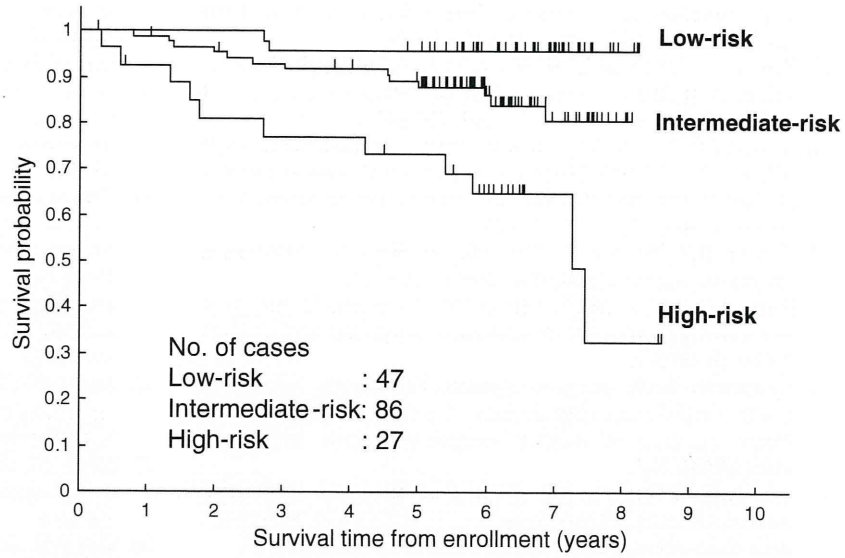


**Fig. 4** Overall survival among patients with HL excluding those with unclassified histopathology according to the number of unfavorable prognostic factors (male and elevated serum LDH). Low risk, intermediate risk and high risk indicate 0, 1 and 2 risk factors, respectively. Data on serum LDH were not available in one patient, and this patient was excluded from this analysis

everybody wants to know the prognostic state of patients with advanced HL treated with state-of-the-art therapy. In our study, eligible patients for the prognostic analysis are almost same as patients for the original IPS study. Then, our prognostic model could be accepted for general use, although further studies should be warranted to validate our prognostic model.

Unfortunately, data on the β2-microglobulin level of 56 patients were missing. In univariate analysis, β2-microglobulin was found to be highly significant in 111 patients. However, multivariate analysis including β2-microglobulin revealed that there was no significant factor detected. Then, β2-microglobulin was excluded from the final multivariate analysis for OS. Serum β2-microglobulin levels are known to reflect renal function and membrane turnover, the latter of which is associated with tumor mass and growth rate. Elevated β2-microglobulin level was reported to predict poor survival in several hematological malignancies including low-grade lymphoma [29], large cell lymphoma [30] and HL [31–33]. Interestingly, Vassilakopoulos et al. [33] reported that the β2-microglobulin level was a powerful independent prognostic factor for OS, but not for failure-free survival in optimally treated patients with HL. The prognostic impact of β2-microglobulin on OS should be re-evaluated in future.

In conclusion, despite the limitation of a small number of patients, our prognostic model was considered to be a simple method of predicting OS in Japanese patients with advanced HL. Further studies to validate our prognostic model and to re-evaluate the prognostic impact on OS of sex and serum LDH combined with β2-microglobulin are warranted.

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# 分子標的治療薬の評価

Clinical trial designs for evaluation of target-based drugs

山本精一郎

Key words：分子標的薬，研究デザイン，個別化治療，予後因子，予測因子

## 1. 分子標的治療薬の評価とは

分子標的治療薬を臨床試験により評価すること，すなわち分子標的治療薬の治療開発の研究デザインはこれまでの細胞障害性薬剤の治療開発と大きく変わるものではない．あえて挙げるとすれば，分子標的薬は，もともと特定の治療ターゲットの存在を想定して開発された薬剤であるので，治療開発の過程で治療効果が現れる集団を同定しながら治療開発を進める必要があるということであろう．分子標的薬の場合，対象を特定せずに治療開発を行い，広い対象に対して標準治療との比較試験を行うと，効果のない対象を含んでしまったために標準治療との間で治療効果の差を検出できず，特定の対象に対して高い効果のある薬剤の開発を中止してしまうということが起こる可能性がある．別の言い方をすると，効果のある対象でなく，効果のない対象をうまく除外することによって薬剤の力を適切に評価するということが重要であるといえる．しかしながら，効果のある対象を除外しないことも重要である．

これは，これまでの細胞障害性薬剤においても，特に治療効果が高いサブグループを探索する，治療効果のないサブグループを同定する，という試みの中で行われてきたことである．そこで本稿では，治療効果の異なるサブグループを探索するという観点から，これまで実施されてきた，あるいは現在計画中の臨床試験を例にしながら，分子標的薬評価のための臨床試験デザインの立て方について考えてみたい．換言すれば，個別化治療開発の臨床試験デザインについて，著者の整理を紹介することを本稿の目的としたい．

## 2. 個別化治療評価にはランダム化比較試験が必要

治療効果の異なる集団を同定するためには，その集団を特定するマーカーが必要となる．このようなマーカーを予測因子（または治療効果予測因子）と呼ぶ．すなわち，予測因子となるマーカーを探すことが個別化治療を進めることであるともいえる．統計的にはこれを‘予後に関して治療とマーカーの間に交互作用あり’という．これに対して，治療を受けていない場合に予後を予測するマーカーを予後因子と呼ぶ．このように予後因子，予測因子を明確に区別することは，個別化治療開発を考えるうえでの理解の助けとなる．

**図1**に予後因子，予測因子の別を示す．マーカーが予測因子であるためには，少なくともどこかの群では治療効果があることを示す必要がある．これは，少なくともどこかの群でランダム化比較試験を行う必要があることを示し

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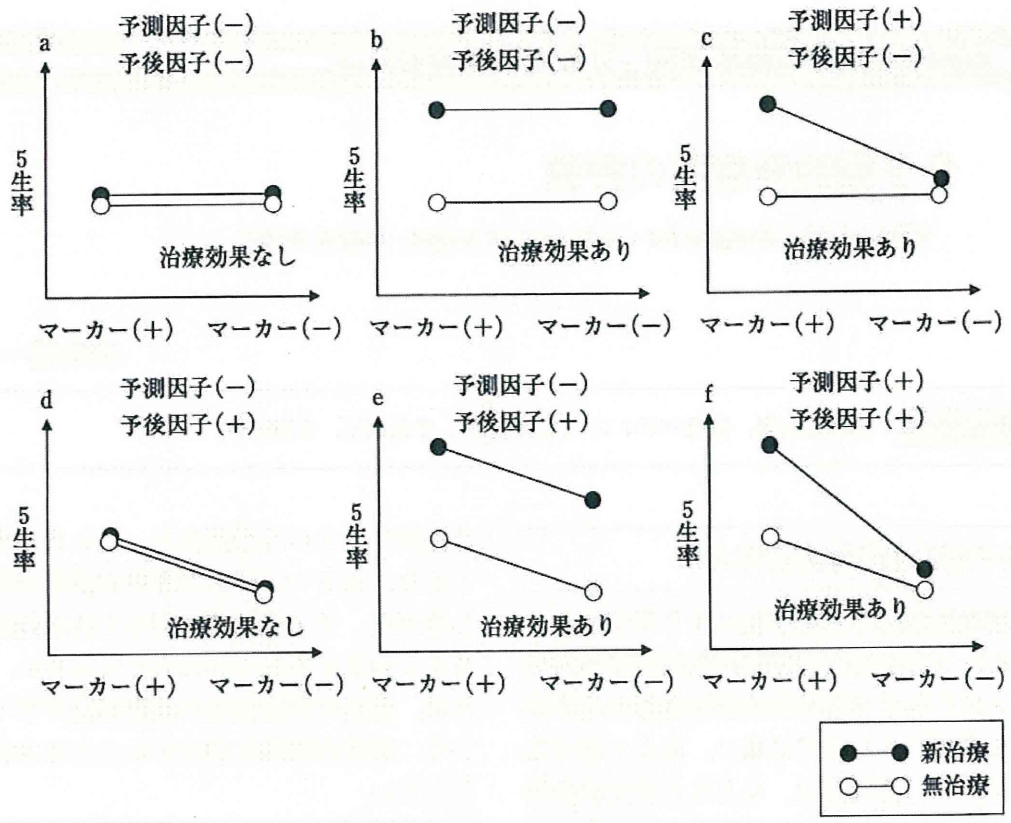


**図1 予測因子と予後因子**

ている.

## 3. 個別化治療開発のためのランダム化比較試験デザイン

### a. Marker(+) design

予測因子を探すという考えに基づく個別化治療開発に対して，大きく分けて3種類の臨床試験デザインが提案されている(**図2**)[1]．まず一つ目は'marker(+) design'といえるもので，マーカーを測定し，(+)の人だけをランダム化して新治療と標準治療を行うものである．いわゆるenrichment designもこのデザインの一種といえる．大きな効果を予測できるマーカー(+)の集団のみ臨床試験を行うようなenrichmentの場合には試験を行う賛同は得られやすいかもしれない．enrichmentの場合，マーカー(−)の集団には治療効果がないことを想定しているか，あっても小さいであろうことを想定している．しかし，マーカー(+)の集団で治療効果が観察されても，マーカー(−)に対しては情報が得られないので，enrichmentだけではマーカーが予測因子かどうかわからないし，もしマーカー(−)のサブグループで治療効果がある場合には，その対象の患者に有効な治療を提供できないことになる．それを解消するために，最初の比較試験ではenrichした対象で比較し，治療効果が証明されればマーカー(−)の集団で開発を行うというストラテジーも考えられるかもしれない．

PottiらはStage IAの非小細胞肺癌に対し，手術時に得られた組織における遺伝子発現を用いてその後の予後を予測する予測モデルを構築した[2]．それにより，再発高リスク群と低リスク群に分けることができるとし，この予測モデルを用いて新たな臨床試験を行うことを提唱している(**図3**)(現在実施中とのこと，私信)．同じStage IAの患者でも，彼らのモデルにより分類された低リスク群の予後は十分によいが，高リスク群の予後はかなり悪く，この群に対しての新たな治療開発が必要だと考えられる．したが

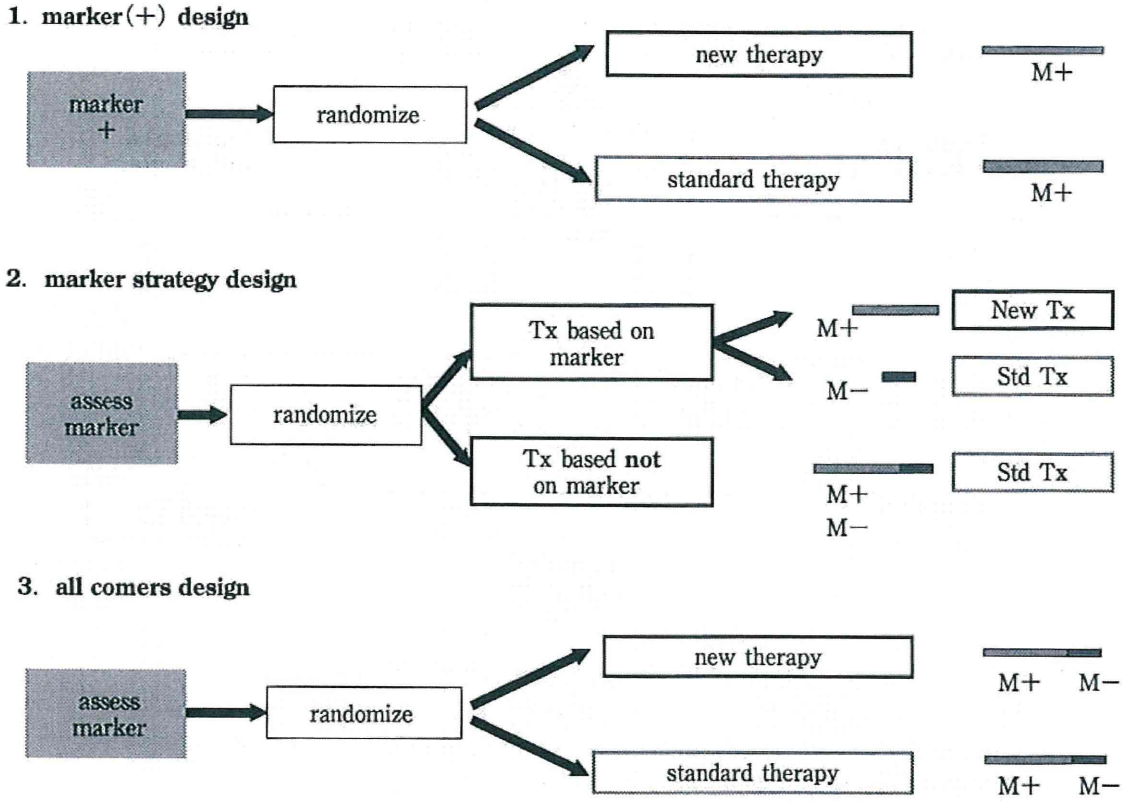


図2 分子標的薬開発に有効として提案されている臨床試験デザイン

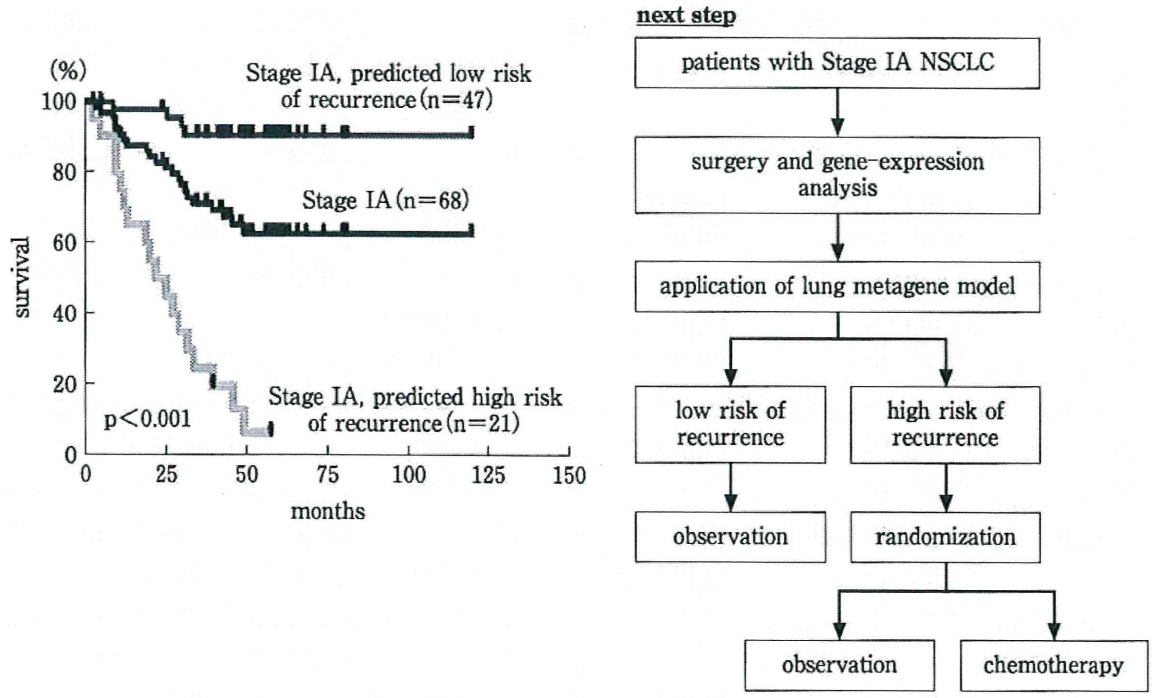


図3 Marker(+) designの例1