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A Randomized Trial Comparing Postoperative Adjuvant Chemotherapy with Cisplatin and 5-fluorouracil versus Preoperative Chemotherapy for Localized Advanced Squamous Cell Carcinoma of the Thoracic Esophagus (JCOG9907)

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The authors of the manuscript “A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907) ” have declared no conflicts of interest.

Running Head : Pre vs. postoperative chemotherapy for ESCC

Synopsis :

Patients with clinical stage II/III esophageal squamous cell carcinoma were randomly assigned to undergo surgery followed or preceded by chemotherapy consisting of two courses of cisplatin plus 5-fluorouracil. Preoperative chemotherapy group showed superior overall survival than postoperative chemotherapy group.

ABSTRACT

Background: Patients with esophageal carcinoma receiving postoperative chemotherapy showed superior disease-free survival than those receiving surgery alone in a Japan Clinical Oncology Group trial (JCOG9204). The purpose of this study is to evaluate optimal perioperative timing, i.e. before or after surgery, for implementing chemotherapy in patients with locally advanced esophageal squamous cell carcinoma.

Methods: Eligible patients with clinical stage II or III, excluding T4, squamous cell carcinoma were randomized to undergo surgery followed (Post group) or preceded (Pre group) by chemotherapy consisting of two courses of cisplatin plus 5-fluorouracil. The primary endpoint was progression-free survival.

Results: We randomized 330 patients, with 166 assigned to the Post group and 164 to the Pre group between May 2000 and May 2006. The planned interim analysis was conducted after completion of patient accrual. Progression-free survival did not reach the stopping boundary, but overall survival in the Pre group was superior to that of the Post group ($p = 0.01$). Therefore, the Data and Safety Monitoring Committee recommended early publication. Updated analyses showed the 5-year overall survival to be 43% in the Post group and 55% in the Pre group (hazard ratio 0.73, 95% confidence interval 0.54-0.99; $p=0.04$), where the median follow-up of censored patients was 61.6 months. Concerning operative morbidity, renal dysfunction after surgery in the Pre group was slightly higher than in the Post group.

Conclusions: Preoperative chemotherapy with cisplatin plus 5-fluorouracil can be regarded as standard treatment for patients with stage II/III squamous cell carcinoma.

INTRODUCTION

Esophageal carcinoma is a formidable disease with possible distant failure even if loco-regional disease is controlled successfully by means of radical surgery. A randomized controlled trial by the Japan Clinical Oncology Group (JCOG9204) comparing postoperative adjuvant chemotherapy using cisplatin plus 5-fluorouracil with surgery alone, showed superior disease-free survival in the postoperative chemotherapy group [1]. In Western countries, preoperative chemoradiotherapy is one of the standard treatments, but the results of the JCOG9204 study showed far better survival than that of those trials [2-4]. In addition, loco-regional tumor recurrence was observed in less than half of all cases of recurrence in the JCOG9204. We therefore speculated that aggressive esophageal cancer surgery in Japan is one plausible reason for the lower local recurrence rate, and therefore eradication of systemic micrometastasis by preoperative chemotherapy followed by aggressive surgery may be a more promising strategy than reinforcement of local tumor control by chemoradiotherapy.

Concerning preoperative chemotherapy, a randomized controlled study in the UK demonstrated that preoperative chemotherapy was superior to surgery alone in overall survival in patients with esophageal carcinoma of any cell type [5,6]. On the other hand, another randomized study in the US showed no survival benefit for preoperative chemotherapy compared with surgery alone [7,8]. Therefore it is still controversial whether preoperative chemotherapy can improve the survival of patients with esophageal squamous cell carcinoma and/or adenocarcinoma compared with surgery alone or postoperative chemotherapy [9]. The objective of this multi-institutional randomized controlled trial was to evaluate the survival benefit of preoperative chemotherapy with cisplatin plus 5-fluorouracil compared with postoperative chemotherapy in patients with locally advanced esophageal squamous cell carcinoma.

PATIENTS AND METHODS

Eligibility

The eligibility criteria for entering this study were as follow: histologically proven squamous cell carcinoma of the thoracic esophagus; c-stage II or c-stage III excluding T4 (UICC TNM classification [10]); resectable disease; age 75 years or younger; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; no previous chemotherapy nor radiotherapy for any malignancies; sufficient organ function and written informed consent. Upper gastrointestinal endoscopy, esophagography, and either CT or MRI were mandatory, and EUS was recommended for clinical staging. The study protocol was approved by the Protocol Review Committee of JCOG and the institutional review board of each participating institution.

Randomization

After the confirmation of the eligibility criteria, the patients were randomized at the JCOG Data Center into either the postoperative chemotherapy group (Post group) or the preoperative chemotherapy group (Pre group). In the Post group, surgery was followed by chemotherapy after 2 to 10 weeks, and in the Pre group, chemotherapy was followed by surgery within 5 weeks. A minimization method was used to balance institution and clinical lymph node status (cN0 vs. cN1).

Surgery

All patients underwent total or subtotal thoracic esophagectomy and regional lymphadenectomy with curative intent. Either right or left thoracotomy was acceptable. Thoracoscopic esophagectomy was acceptable but transhiatal esophagectomy was not [11]. Regional lymph nodes included not only mediastinal (paraesophageal, paratracheal, subcarinal, supradiaphragmatic and posterior mediastinal lymph nodes) but also perigastric nodes. Dissection of distant lymph nodes such as cervical nodes, i.e. a three-field

lymphadenectomy , or celiac nodes, was optional [12]. Esophageal reconstruction was performed using the stomach, colon, or jejunum.

Chemotherapy

Chemotherapy with cisplatin plus 5-fluorouracil was repeated twice every 3 weeks in each arm. A dose of 80 mg/m^2 cisplatin was given by intravenous drip infusion for 2 hours on day 1; 5-fluorouracil was administered at a dose of 800 mg/m^2 by continuous infusion on days 1 through 5.

In patients with node-negative status (pN0) resected specimens in the Post group, chemotherapy was not given postoperatively, based on the result of our former study (JCOG9204). In patients whose response to the first course of chemotherapy was progressive disease in the Pre group, a second course of chemotherapy was not given, in order to take advantage of the probability for curative resection.

Study Design and Statistical Analysis

The primary endpoint was progression-free survival, as in the preceding study. The secondary endpoints were overall survival, chemotherapy toxicities, operative morbidity and mortality, response rate in the Pre group and complete resection rate. The expected 5-year progression-free survival in the Post group was 50%. This study was designed to randomize 330 patients to detect about 13% improvement in 5-year progression-free survival in the Pre group with a one-sided alpha error of 0.05 and a power of 0.80. The planned accrual and follow-up period was 4 and 3 years.

Overall survival was measured from the date of randomization to the date of death, or last follow-up. Progression-free survival was measured from the date of randomization to the date of first evidence of relapse or death due to any cause, whichever was observed first. For patients who had not relapsed or died, progression-free survival was censored at the last date at which the absence of relapse was confirmed. Overall and progression-free survival curves

were calculated by the Kaplan-Meier method. Confidence intervals (CI) of survival distribution were based on the Greenwood's formula. Stratified Cox regression analysis with clinical lymph node status as a stratification variable was carried out to estimate the hazard ratio in the primary analysis of progression-free survival, and unstratified Cox regression analyses were applied for the other analyses. This study was designed and conducted on the basis of one-sided testing, and the results are presented with two-sided P values. All the statistical analyses were performed with SAS software release 9.1 (SAS Institute, Cary, NC) by the JCOG Data Center. This study was registered with ClinicalTrials.gov, identification number NCT00190554.

Clinicopathologic parameters are expressed according to the TNM Classification of the International Union Against Cancer (UICC) [10]. The clinical response was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) [13]. Adverse events were classified according to NCI common toxicity criteria (NCI-CTC version 2.0) [14].

RESULTS

Patient Characteristics

Twenty-four leading institutions in Japan participated in this study. During 6 years since May 2000 to May 2006, 330 patients were randomly assigned to either the Post group (166 patients) or the Pre group (164 patients). These patients comprised 11% (330 /3, 092) of all patients with clinical stage II and III esophageal cancer treated in participating institutions during the study, since informed consent was obtained in only 19% (330 /1,716) of all patients who met the eligibility criteria. The characteristics of the two groups were similar. (Table 1)

Disposition of the Patients

The trial profile is shown in Figure 1. In the Post group, 108 patients were resected completely (R0) and diagnosed as pathologic node positive, among which 81 patients (75%)

completed 2 courses of postoperative chemotherapy. Thirty-nine patients were diagnosed as R0 and pN0, therefore all but 1 of that subset (38 patients) did not undergo postoperative chemotherapy, in compliance with the study protocol. In the Pre group, 140 patients (85.4%) completed 2 courses of preoperative chemotherapy and 154 patients underwent surgery.

Surgical Treatment

Transthoracic esophagectomy via right thoracotomy was performed in 157 patients in the Post group and in 149 patients in the Pre group. Left thoracotomy was performed in 1 patient and thoracoscopic esophagectomy in 4 patients in each group. No patient underwent transhiatal esophagectomy without thoracotomy, in compliance with the study protocol.

Toxicities and Tumor Responses to Chemotherapy

Toxicities of chemotherapy were commonly mild and were observed slightly more frequently in the Post group. The incidences of major grade 3 or 4 adverse events in the Post and Pre groups were 5% and 3% for leukopenia, 2% and 1% for thrombocytopenia, 2% and 1% for diarrhea, and 8% and 3% for mucositis. No patient died of causes related to chemotherapy.

Complete responses to preoperative chemotherapy were observed in 4 patients and partial responses in 58 patients, therefore the clinical response rate of preoperative chemotherapy was 38% (95%CI: 30.4-45.7%).

Operative Morbidity and Mortality

Median intraoperative blood loss was 446 ml in the Post group and 450 ml in the Pre group. In the Pre group, renal dysfunction after surgery (9 patients, 6%) was slightly more frequent than in the Post group (4 patients, 3%). There were no remarkable differences between two groups in terms of other postoperative complications. One patient in each group died of causes related to surgery (esophago-bronchial fistula on the 12th postoperative day in the Post group, aortic perforation on the 8th postoperative day in the Pre group).

Progression-free and Overall Survival

The planned 1st interim analysis was done in March 2004 at the midpoint of patient accrual and the planned 2nd interim analysis was performed in March 2007 after completion of patient accrual. At the 2nd interim analysis, the information time was 78% (observed/expected number of events=159/205) and the corresponding threshold for the p-value was one-sided 0.02 (two-sided 0.04). The primary analysis compared progression-free survival and its one-sided stratified log-rank p-value was 0.04 (two-sided p-value was 0.08). The hazard ratio of the Pre group compared with the Post group was 0.76 with multiplicity adjusted 95% (unadjusted 94.9%) CI, 0.56 to 1.04.

Even though the Pre group showed better tendency in progression-free survival, the primary endpoint progression-free survival did not meet the pre-specified stopping criterion. However, a large difference between two groups was observed in overall survival (p=0.01, unstratified log-rank test; hazard ratio 0.64; 95% CI, 0.45 to 0.91). The Data and Safety Monitoring Committee recommended early publication. The results of the final analyses in May 2009 for progression-free survival and overall survival are shown in Figure 2 and 3. The median follow-up of censored patients was 62 months (range: 10.7-106.8). The 5-year progression-free survival was 39% (95% CI, 31.3 to 46.3) in the Post group and 44% (95% CI, 36.4 to 51.8) in the Pre group (p = 0.22). The unstratified hazard ratio of the Pre group to the Post group was 0.84 (95% CI, 0.63 to 1.11). The 5-year overall survival was 43% (95% CI, 34.6 to 50.5) in the Post group and 55% (95% CI, 46.7 to 62.5) in the Pre group (p = 0.04). The unstratified hazard ratio of the Pre group to the Post group was 0.73 (95% CI, 0.54 to 0.99, p=0.04).

We gave some treatments for progression to 72 patients (43%) in the Post group and 76 patients (46%) in the Pre group. Slightly more underwent a subsequent surgical treatment for progression in the Pre group (12 patients, 7%) than the Post group (6 patients, 4%).

Subgroup analysis

The results of subgroup analyses of overall survival regarding clinical lymph node status, clinical tumor depth, clinical stage, performance status and tumor location are shown in Figure 4. Treatment was more effective in the Pre group in clinical stage II cases, cases involving the upper and the middle third of the esophagus, or cases invading less deep layers.

Down-staging and Curability

Data on the distribution of baseline clinical stage, pathological stage, and surgical curability are shown in Figure 5. While the baseline clinical stages were similar, there were more pathologic stage II or lower cases in the Pre group (48%) than the Post group (33%). The proportion of patients with cN0 in both groups was almost identical (34% in the Post group and 35% in the Pre group), while pN0 was seen in 24% in the Post group and 33% in the Pre group. Stage IV due to M1/LYM was less frequent in the Pre group (12%) than the Post group (19%). There were slightly more patients completely resected (R0) [15] among patients who underwent surgery in the Pre group (96%) than the Post group (91%).

DISCUSSION

Our study demonstrated that adjuvant chemotherapy should be induced before surgery rather than after surgery in patients with squamous cell carcinoma of the thoracic esophagus. There are 3 possible reasons for the better preoperative chemotherapy results. First, down-staging was achieved in some patients by preoperative chemotherapy. While the proportion of the patients with clinical stage II was similar in the 2 groups, the proportion with pathologic stage II or lower stage was higher in the Pre group. Secondly, complete resection (R0) was slightly more frequent in the Pre group than the Post group. Thirdly, the completion of protocol treatment was much better in the Pre group than the Post group. Treatment according to the protocol with two courses of chemotherapy and R0 resection was done in 85% of the Pre

group patients, but only in 75% in the Post group. These results suggest it is not difficult to perform preoperative chemotherapy in esophageal cancer surgery candidates.

In our previous study (JCOG9204), less than half of all recurrences were loco-regional, and therefore chemoradiotherapy was not chosen as the test treatment arm in the present study. Patients with a single loco-regional tumor recurrence in the present study consisted of 31% of patients with tumor recurrence in the Post group and 25% in the Pre group. The lower rate of loco-regional recurrence in the present study may result from our meticulous surgical procedure. Our standard surgical procedure was transthoracic esophagectomy with regional lymphadenectomy. The results of our study suggest that preoperative chemotherapy is a good treatment strategy if sufficient local tumor control is achieved by aggressive surgical procedures, and improves overall survival for patients with squamous cell carcinoma. On the contrary, if local tumor control is insufficient, more aggressive adjuvant therapy such as preoperative chemoradiotherapy may be a preferable treatment modality. The clinical question of which is better, preoperative chemotherapy or preoperative chemoradiotherapy, still needs to be clarified [16], and now we are planning the next clinical trial to resolve that question.

Numerous reports have been devoted to adjuvant chemotherapy for esophageal cancer especially concerning controversies in terms of optimal timing, or indications according to histologic type. Kelsen, et al reported that preoperative chemotherapy with cisplatin and fluorouracil did not improve overall survival compared with surgery alone [7,8]. More than half of their cases were adenocarcinoma, and the proportion of R0 resection was only about 60% in each arm. The difference from the results of our study, may allow speculation that preoperative chemotherapy with cisplatin and fluorouracil might be too weak to complement loco-regional tumor control if R0 resection is not achieved. On the other hand, the Medical Research Council found that preoperative chemotherapy with the same combination improved survival relative to outcome with surgery alone in a study of 802 patients. In the MRC study,

30% of patients treated with surgery alone underwent incomplete resection, and survival in the group with surgery alone was unusually poor (median, 13 months) [5]. Since these two pivotal studies demonstrated completely different conclusions, the benefit of preoperative chemotherapy even limited to patients with esophageal squamous cell carcinoma was controversial before our study, even though a recent meta-analysis showed a benefit of preoperative chemotherapy in patients with adenocarcinoma, but not in patients with squamous cell carcinoma [17].

The subgroup analysis suggested better survival superiority in the Pre group depending on the site of tumor location, i.e. better results were obtained in higher esophageal site than in the lower esophagus. The middle third of the esophagus is the most frequent site of esophageal squamous cell carcinoma in Japan [18] and such cases tend to metastasize to not only the lower mediastinal and perigastric nodes but the upper mediastinal and cervical nodes. Therefore upper mediastinal lymphadenectomy is necessary [19], but is less likely to be carried out thoroughly than lower mediastinal and perigastric lymphadenectomy due to anatomical limitations. Preoperative chemotherapy could overcome lack of loco-regional tumor control by upper mediastinal lymphadenectomy.

One controversy of our study is the protocol treatment in the Post group in which the postoperative chemotherapy is not given to pN0 patients. In our preceding JCOG9204, the disease-free survival showed little difference between the surgery-alone group and the surgery-plus-postoperative chemotherapy group in the pN0 subgroup: 5-year disease-free survivals were even better in the surgery-alone group (76%) than the postoperative chemotherapy group (70%), hazard ratio of the postoperative chemotherapy group to the surgery-alone group was 0.94 (95% CI, 0.35 to 2.50). When planning the present study, giving chemotherapy after surgery for pN0 patients with comparatively good prognosis was not acceptable in the community considering the benefit / risk ratio and our group members

reached an agreement that the standard treatment for pN0 patients should be surgery alone. Such patient selection based on pathologic findings would be one advantage of postoperative chemotherapy especially when clinical nodal status is not necessarily concordant with pathological status. Furthermore, the 5-year overall survival of pN0 patients undergoing no postoperative chemotherapy in the Post group was not bad (64%), while that of pN1 patients who were unable to undergo postoperative chemotherapy in the Post group was dismal (0%). That means the former group (i.e. pN0 with no postoperative chemotherapy) was not the main reason for the poor outcome in the Post group, rather it was the latter (i.e. pN1 who were unable to undergo postoperative chemotherapy for the various reasons) that essentially compromised the overall survival in the Post group.

Another controversy of our study, regarding the interpretation of the results, is the discrepancy between progression-free survival and overall survival where overall survival showed larger difference than progression-free survival. Longer survival after progression in the Pre group is one of the possible explanations for this discrepancy. This may have resulted because more patients in the Pre group who underwent a subsequent surgical treatment for progression. Since progression-free survival is not a validated surrogate endpoint of overall survival, we should have adopted overall survival as the primary endpoint. Our Data and Safety Monitoring Committee discussed this issue and decided to recommend early publication based on the large difference observed in overall survival by means of true endpoint directly reflecting patient benefit.

In conclusion, preoperative chemotherapy with cisplatin plus 5-fluorouracil followed by surgery improved overall survival without additional serious adverse events. Preoperative chemotherapy with cisplatin plus 5-fluorouracil can be regarded as a new standard treatment modality for patients with Stage II/III esophageal squamous cell carcinoma.

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FIGURE LEGENDS

Figure 1: Disposition of the patients

Cx = chemotherapy.

Figure 2: Progression-free Survival

Pre group = preoperative chemotherapy, Post group = postoperative chemotherapy.

Figure 3: Overall survival

Pre group = preoperative chemotherapy, Post group = postoperative chemotherapy.

Figure 4: Tests for heterogeneity of treatment effect according to the clinical characteristics of the patients

PS = Performance status. Upper = the upper third of the esophagus as the site of the primary tumor, Middle = the middle third, Lower = the lower third.

Figure 5: Down-staging and differences of curability by means of preoperative chemotherapy

* R0 sub-classification by Japanese Society for Esophageal Cancer

Degree A ; D > pN, Degree B ; other R0

Table 1. Patient Characteristics (All randomized)

		Post n= 166	**Pre** n=164
Age			
	median (range)	61 (39-75)	61 (34-75)
Gender			
	male	153	144
	female	13	20
PS (ECOG)			
	0	122	123
	1	44	41
Location of primary tumor			
	upper	16	12
	middle	79	87
	lower	71	65
Clinical TNM (UICC)			
	T1	5	6
	T2	37	35
	T3	124	123
	N0	54	58
	N1	112	106
	M0	165	164
	M1	1*	0
Clinical Stage (UICC)			
	II	79	82
	III	86	82
	IV	1*	0

* Cervical node metastasis by CT was overlooked before registration.

Fig.1

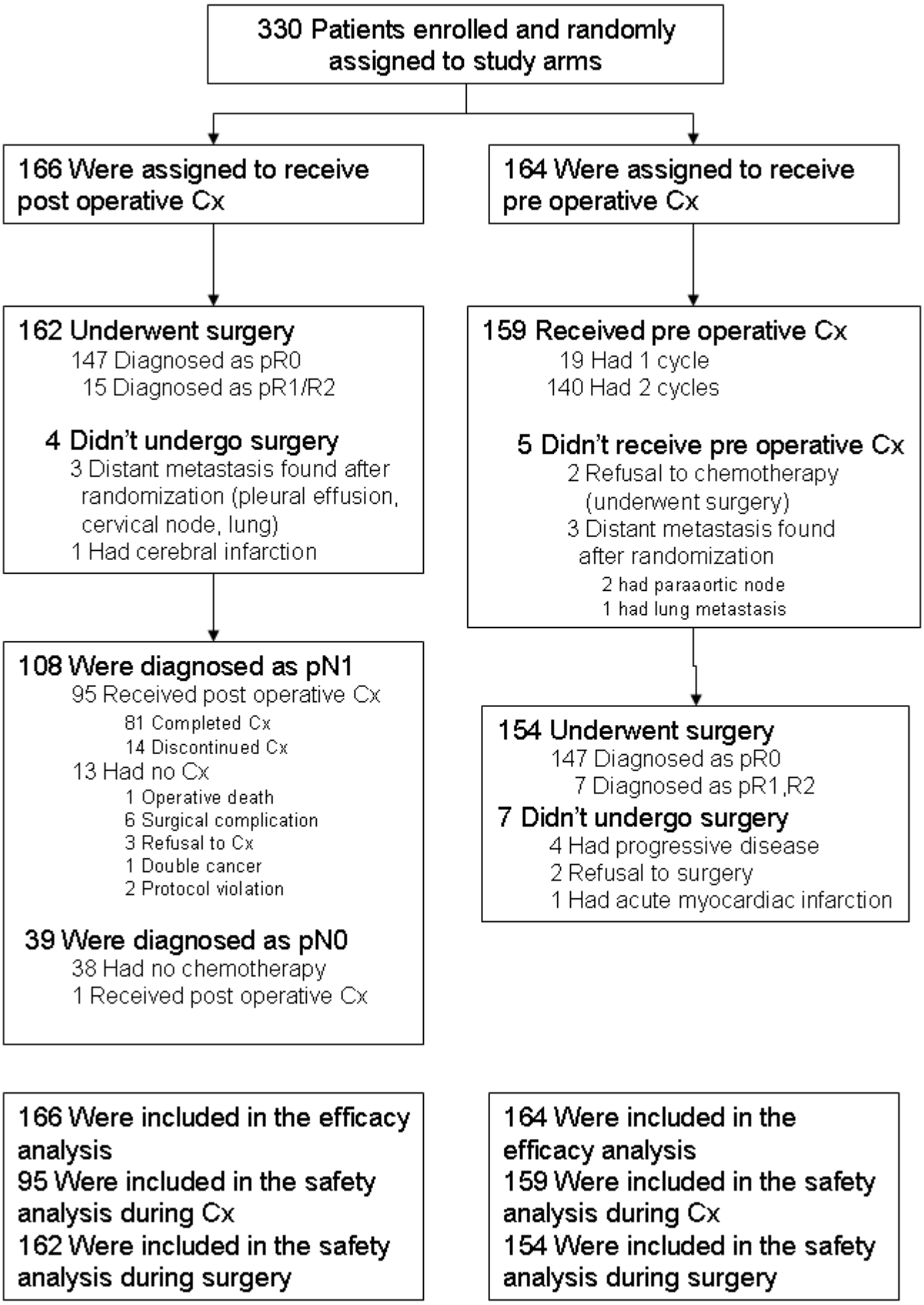
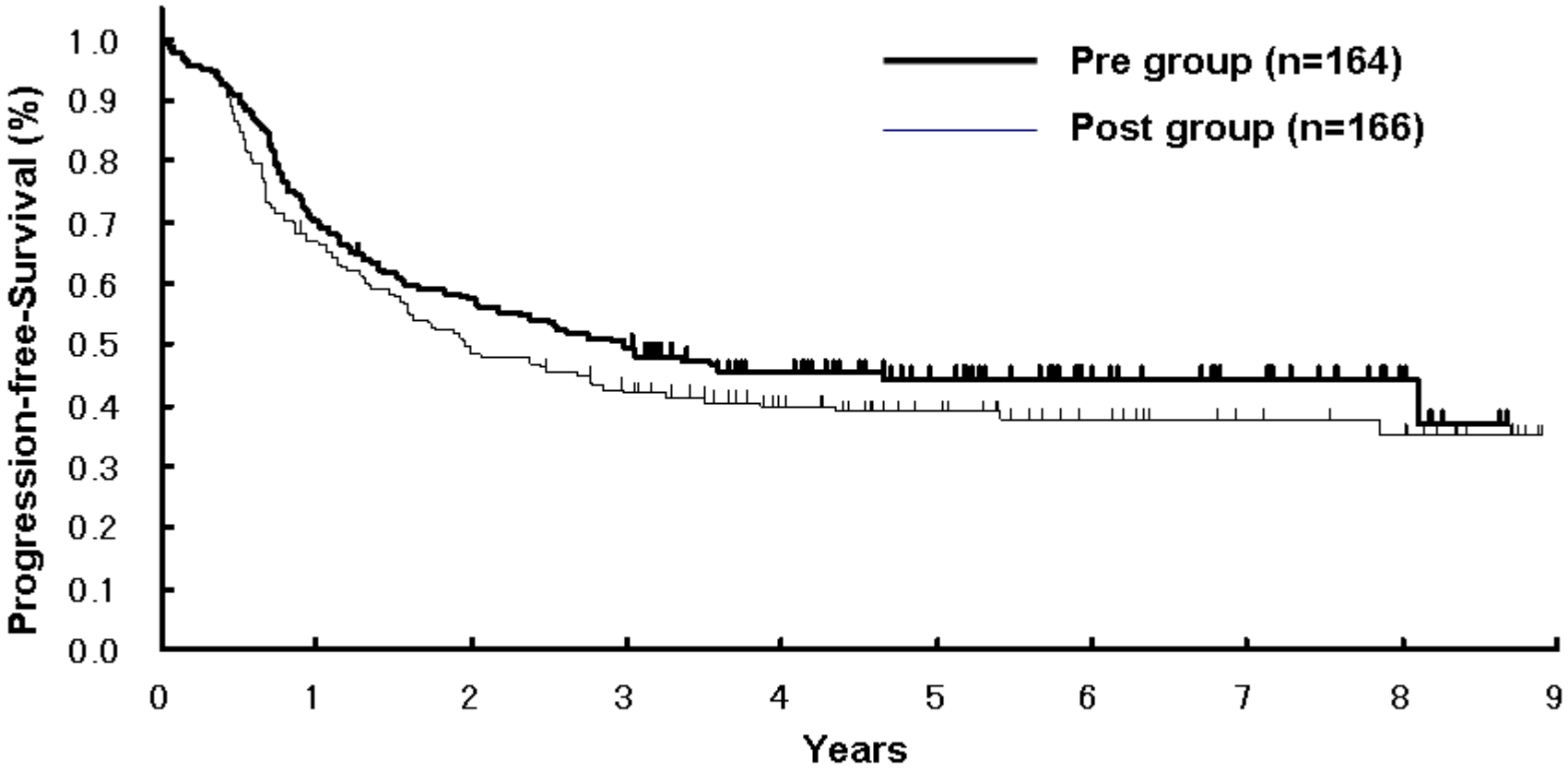

330 Patients enrolled and randomly assigned to study arms
166 Were assigned to receive post operative Cx
164 Were assigned to receive pre operative Cx
162 Underwent surgery
147 Diagnosed as pR0
15 Diagnosed as pR1/R2
4 Didn't undergo surgery
3 Distant metastasis found after randomization (pleural effusion, cervical node, lung)
1 Had cerebral infarction
159 Received pre operative Cx
19 Had 1 cycle
140 Had 2 cycles
5 Didn't receive pre operative Cx
2 Refusal to chemotherapy (underwent surgery)
3 Distant metastasis found after randomization
2 had paraaortic node
1 had lung metastasis
108 Were diagnosed as pN1
95 Received post operative Cx
81 Completed Cx
14 Discontinued Cx
13 Had no Cx
1 Operative death
6 Surgical complication
3 Refusal to Cx
1 Double cancer
2 Protocol violation
39 Were diagnosed as pN0
38 Had no chemotherapy
1 Received post operative Cx
154 Underwent surgery
147 Diagnosed as pR0
7 Diagnosed as pR1,R2
7 Didn't undergo surgery
4 Had progressive disease
2 Refusal to surgery
1 Had acute myocardiac infarction
166 Were included in the efficacy analysis
95 Were included in the safety analysis during Cx
162 Were included in the safety analysis during surgery
164 Were included in the efficacy analysis
159 Were included in the safety analysis during Cx
154 Were included in the safety analysis during surgery

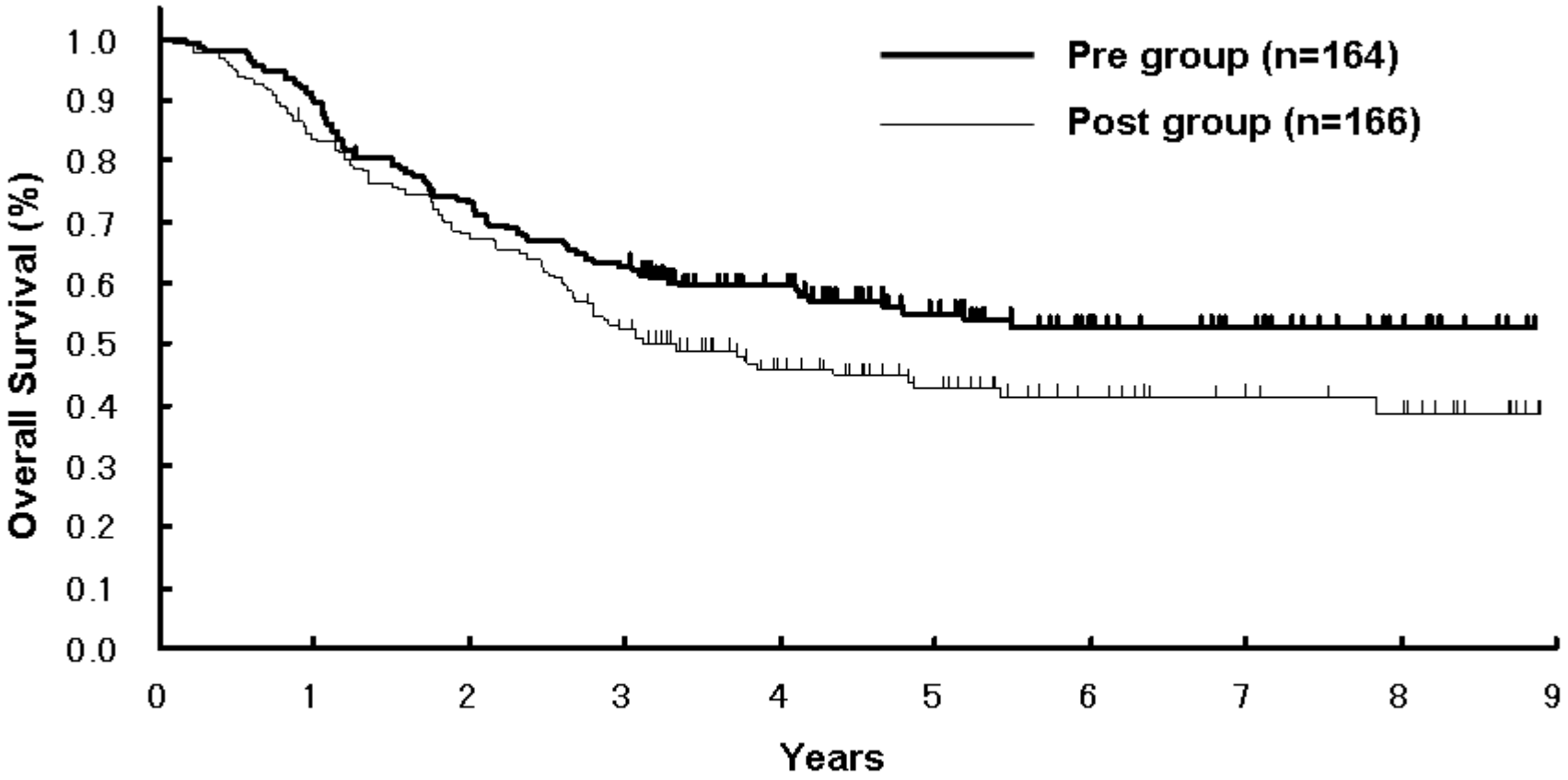
Fig.2



No. at risk

Post group	166	110	80	66	49	35	24	17	14
Pre group	164	115	93	80	59	42	25	18	7

Fig.3



No. at risk

Post group	166	138	112	84	55	38	24	17	14
Pre group	164	147	119	102	76	53	30	22	11

Fig.4

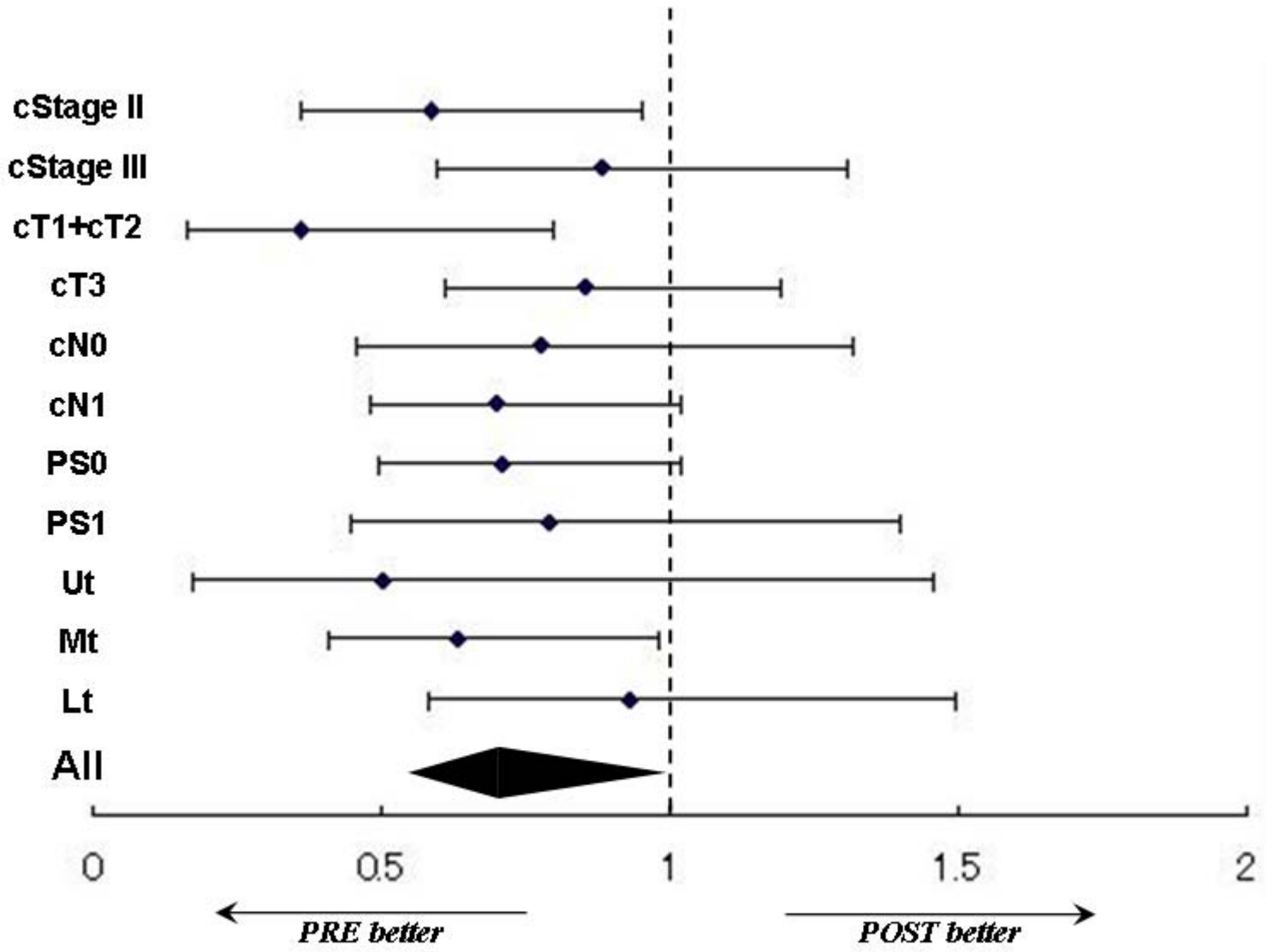
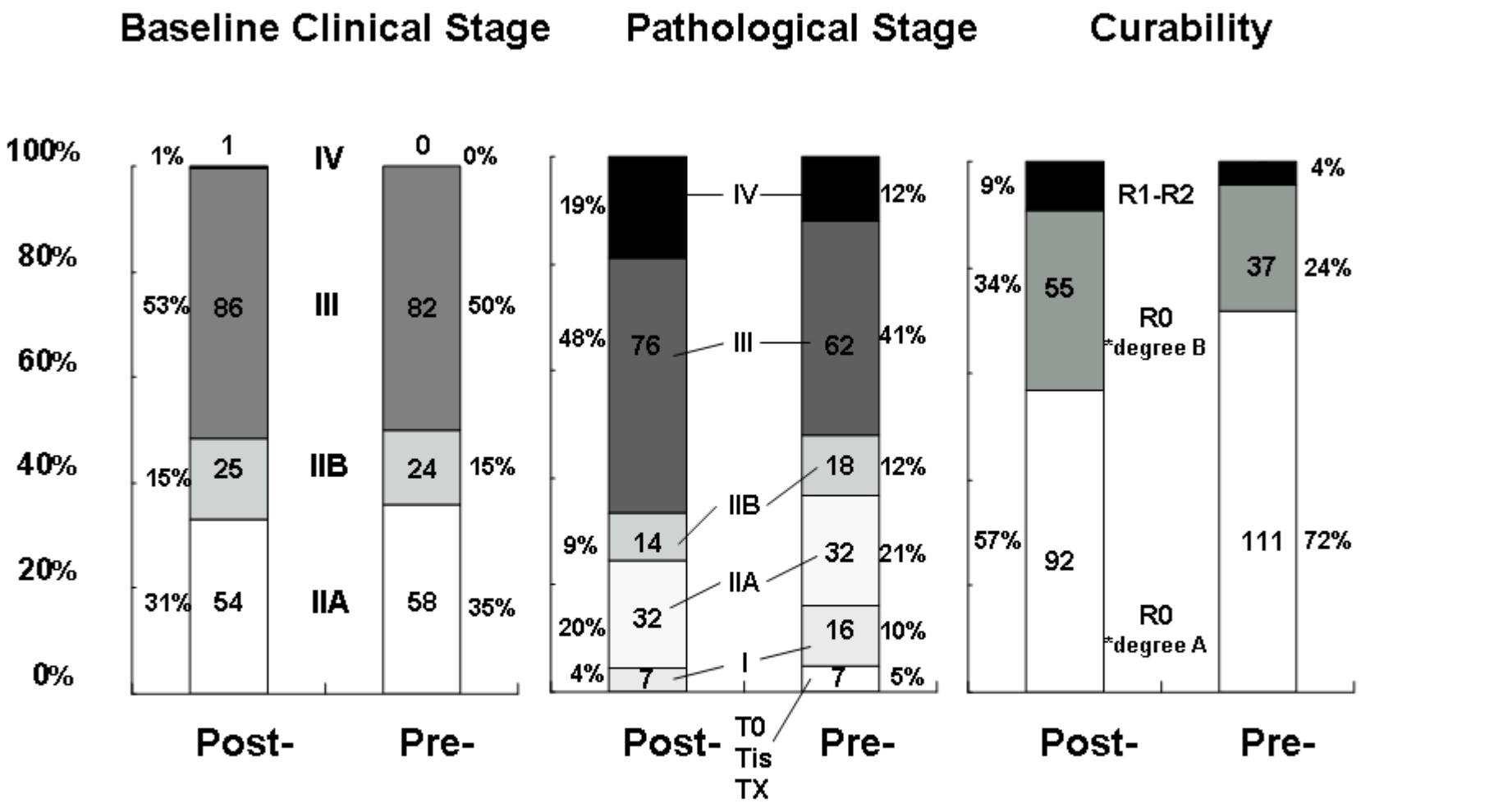

cStage II
cStage III
cT1+cT2
cT3
cN0
cN1
PS0
PS1
Ut
Mt
Lt
All
0
0.5
1
1.5
2
PRE better
POST better

Fig.5



*** R0 sub-classification by Japanese Society for Esophageal Diseases[12]: Degree A, D > pN; Degree B, other R0.**