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Multi-center retrospective study of the prognosis and the effect of postoperative adjuvant therapy in Japanese oral squamous cell carcinoma patients with close margin

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CONFLICTS OF INTEREST

We declare no conflict of interest associated with this manuscript.

ABSTRACT

Background: The purpose of this retrospective study was to investigate the prognosis of patients with oral cavity cancer with positive margin (PM) or close margin (CM) divided into pN- and pN+ groups.

Methods: The evaluated endpoints were local control and disease-specific survival (DSS) rates.

Results: Higher T classification, lymphovascular space invasion (LVSI), and older age were significant risk factors for DSS in the pN- groups. On the other hand, extranodal extension, multiple lymph node metastases, and LVSI were significant risk factors for DSS in the pN+ groups. Among the CM pN+ patients, no significant differences in the three-year DSS were observed between the only surgery (51.9%) and adjuvant groups (53.2%).

Conclusions: Higher T classification and LVSI are high risk features more than PM or CM in the pN- groups for DSS. However, further prospective studies are needed to demonstrate the usefulness of adjuvant treatment in patients with PM or CM.

INTRODUCTION

Recently, treatments for advanced oral squamous cell carcinoma (OSCC) have improved. Surgical treatment for resectable advanced OSCC is the most common approach [1-3], and postoperative radiotherapy (RT) with or without chemotherapy is an important adjuvant treatment for advanced OSCC. The postoperative treatment principles of OSCC are based on two randomized trials for head and neck squamous cell carcinoma (HNSCC) with high risk of recurrence [4, 5]. However, the definition of a high-risk feature with regard to margin differs between the two trials. In the RTOG trial [5], the definition was positive margin (PM), whereas in the EORTC trial it was close margin (CM; < 5 mm) [4]. Therefore, in the collaborative comparative analysis of these two randomized trials, only PM and extranodal extension (ENE) of neck lymph nodes were defined as major high risk factors for recurrence, and the addition of concomitant cisplatin (CDDP) to postoperative RT improved outcomes including overall survival (OS) in HNSCC patients with one or the combination of two major prognostic factors [6]. However, clinically, most patients with PM receiving postoperative RT or concomitant chemoradiotherapy (CCRT) simultaneously have ENE or multiple lymph node metastases (MLM). Therefore, OSCC with PM or CM without neck lymph node metastases (pN-) is too rare for a single-institution study. Moreover, because regional lymph node metastasis is the most important prognostic factor, it is unclear whether the postoperative RT/CCRT is effective in pN- patients with PM or CM. In this multicenter study, we retrospectively investigated the prognosis of patients with PM or CM divided into pN- and pN+ groups and identified significant multivariate relationships among risk factors of poor prognosis. And, we compared outcomes between patients who received no postoperative therapy and those who underwent postoperative RT/CCRT.

PATIENTS & METHODS

This was a nonrandomized, multicenter retrospective cohort study. The institutional review board of Kobe University Graduate School of Medicine approved this study. This validation study included pooled individual patient data from seven institutions. Between January 2001 and December 2018, 2395 OSCC cases were investigated at the following institutes: Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine; Department of Oral and Maxillofacial Surgery, School of Medicine, Nara Medical University; Department of Oral and Maxillofacial Surgery, Saiseikai Matsusaka General Hospital; Department of Clinical Oral Oncology, Unit of Translational Medicine, Nagasaki University Graduate School of Biomedical Sciences; Department of Oral and Maxillofacial Surgery, Oita Red Cross Hospital; Department of Oral Surgical Oncology, Hokkaido Cancer Center; and Department of Dentistry and Oral Surgery, Shinshu University School of Medicine. Patients who had undergone neoadjuvant RT or chemotherapy or had inadequate clinical information were excluded. The remaining 2145 patients were eligible for inclusion. Due to the retrospective design of this study, informed consent was not required. Instead, we published the information regarding this study and gave patients opportunities to decline participation in this study. A total of 1217 male and 928 female patients were included. Mean patient age was 66.3 ± 14.1 years (range: 15–99 years). Treatment selection was based on institutional policy or patient preference. Adjuvant radiotherapy was recommended for patients with major (ENE and PM) and minor risks (advanced stage, MLM, level IV/V lymph node involvement, CM, perineural invasion [PNI], and lymphovascular space invasion [LVSI]) in all participating institutions. However, the final decision of adjuvant radiotherapy was made by the surgeons, considering the general condition of the patients and the patients' preferences. Initially, the patients were divided into two groups: pathologically negative lymph nodes (pN-) and positive lymph nodes (pN+). For each group, clinicopathological data, including sex, age, performance status (PS), subsite, clinical T classification (UICC/AJCC staging system 8th edition),

histologic grade (well differentiated, moderately differentiated, or poorly differentiated), pathological node status (ENE and MLM), surgical margin (negative, CM, and PM), timing of neck dissection, and treatment outcome were investigated. Tumor borders were determined by visual inspection and palpation during surgery. An intraoperative frozen section was performed if indicated for the assessment of margin status. Pathological results included the mucosal and deep margin status and the primary tumor size and thickness. CM was defined as a distance of <5 mm between the invasive tumor front and the resected margin. PM was defined as the presence of cancer cells at the resection margin. The evaluated endpoints were local control (LC) and disease-specific survival (DSS) rates. In the CM or PM groups, treatment modalities (surgery only [S only], with postoperative RT/CCRT [S + RT/CCRT]) were investigated. In each group (pN- and pN+), the LC, regional control (RC), distant metastasis control (DM), and DSS rates of the CM and PM groups were compared between S only and S + RT/CCRT. LC, RC, and DM were measured from the date of surgery to the date of first recurrence (local, regional, or distant), respectively, or the last follow-up. DSS was measured from the date of surgery to the date of death or the last follow-up, and patients who died of causes other than oral squamous cell carcinoma were censored at the time of death. Postoperative RT alone was performed using a total of 50–70 Gy. Conventional RT was administered at 2 Gy/day for 5 days/week. Chemotherapy primarily consisted of cisplatin, tegafur-gimeracil-oteracil (S-1), or cetuximab. Cisplatin chemotherapy doses were 80 or 100 mg/m^2 of body surface area and were given on days 1, 22, and 43 during the RT course.

Statistical analysis

Data collection and statistical analyses were carried out with SPSS 15.0 (SPSS, Chicago, IL) and Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan). The association of each variable was tested by using the Mann-Whitney U nonparametric test for ordinal variables and the Fisher’s exact test or Chi-squared test for

categorical variables. Cumulative LC, RC, DM, and DSS were calculated using the Kaplan-Meier product-limit method. The significant levels among the curves were determined using the log-rank test. In each pN- and pN+ group, all of the variables associated with the DSS were introduced into multivariate Cox proportional hazard models by the forward stepwise selection method using the likelihood ratio. Hazard ratio (HR) and 95% confidence intervals (CIs) were also calculated. Probabilities of less than 0.05 were accepted as significant.

RESULTS

Clinicopathological patient characteristics and the LC and DSS rates in each group are summarized in Table 1 and Table 2, respectively. There were more men than women. The most common tumor subsite was oral tongue, followed by lower gingiva. The most common histologic grade was well differentiated. The mean follow-up time among the 2145 patients was 48.1 months (range: 1–226 months). There were 1488 (69.4%) and 657 (30.6%) patients in the pN- and pN+ groups. A total of 171 (11.5%) and 88 (13.4%) patients had CM in the pN- and pN+ groups, respectively. A total of 60 (4.0%) and 40 (6.1%) patients had PM in the pN- and pN+ groups, respectively (Table 1). At the time of the last follow-up, a total of 1320 (88.7%) and 362 (55.1%) patients were alive in the pN- and pN+ groups, respectively. A total of 42 (2.8%) and 66 (10.0%) patients died of local failure in each of the groups, respectively. A total of 5 (0.3%) and 64 (9.7%) patients died of regional failure in each of the groups, respectively. A total of 16 (1.1%) and 79 (12.0%) patients died of distant metastasis in each of the groups, respectively (Table 1). The leading cause of death in the pN- group was other disease (5.6 %), while that in the pN+ group was distant metastasis (12.0%) (Table 1).

In the pN- group, the 3-year cumulative LC rates for the negative margin, CM, and PM groups were 93.8%, 83.0%, and 72.2%, respectively (Figure 1). Negative margin was associated with a better LC rate than that of the CM and PM groups ($P < 0.05$). In the pN- group, the 3-year cumulative DSS rates for the negative margin, CM, and PM groups were 96.8%, 90.8%, and 91.4%, respectively (Figure 1). Negative margin was associated with a better DSS rate than that of the CM groups ($P < 0.05$).

In the pN+ group, the 3-year cumulative LC rates for the negative margin, CM, and PM groups were 83.4%, 68.8%, and 51.8%, respectively (Figure 2). Negative margin was associated with a better LC rate than that of the CM and PM groups ($P < 0.05$), while CM was associated with a better LC rate than that of the PM groups ($P < 0.05$). In the pN+ group, the 3-year cumulative DSS rates for the negative margin, CM, and PM groups were

63.1%, 53.0%, and 48.2%, respectively (Figure 2). Negative margin was associated with a better DSS rate than that of the PM groups ($P < 0.05$).

In the CM, pN- group, 155 and 16 patients received S only and S+RT/CCRT, respectively (Figure 3). The S only group was associated with a better LC rate than the S + RT/CCRT group ($P < 0.05$). In the PM, pN- group, 50 and 10 patients received S only and S + RT/CCRT, respectively (Figure 4). The S only group was associated with better RC, DM, and DSS rates than the S + RT/CCRT group ($P < 0.05$). In the CM, pN+ group, 49 and 39 patients received S only and S + RT/CCRT, respectively (Figure 5). In the PM, pN+ group, 18 and 22 patients received S only and S + RT/CCRT, respectively (Figure 6). In the CM and PM pN+ groups, there were not significant differences between the S only and S + RT/CCRT groups (Figures 5, 6).

In multivariable Cox proportional hazards analysis, higher T classification (HR 4.33, 95% CI 2.14-8.79; $P < 0.001$), LVSI (HR 3.53, 95% CI 1.89-6.61; $P < 0.001$), and older age (HR 3.90, 95% CI 1.90-7.89; $P < 0.001$) were independent predictors of DSS in the pN- group (Table 3). In the pN+ group, ENE (HR 2.24, 95% CI 1.57-3.19; $P < 0.001$), LVSI (HR 1.72, 95% CI 1.19-2.48; $P = 0.004$), CM or PM (HR 1.66, 95% CI 1.11-2.47; $P = 0.013$), and MLM (HR 1.50, 95% CI 1.04-2.15; $P = 0.028$) were independent predictors of DSS (Table 4).

DISCUSSION

Clinically, most patients with PM receiving postoperative RT or CCRT simultaneously have ENE or multiple lymph node metastases (MLM). Therefore, OSCC patients with PM or CM without ENE or MLM receiving postoperative therapy are too rare for research. Furthermore, in the collaborative analysis of two major randomized controlled trials, there were still very few patients with only PM or CM receiving postoperative RT/CCRT: 43 (13 %) in the EORTC trial and 23 (6 %) in the RTOG trial [6]. Therefore, the effect of postoperative RT/CCRT on major risk factors (PM and ENE) in these studies might depend on the factor of regional lymph node metastasis. In this multicenter study, we retrospectively demonstrated the prognosis of patients with PM or CM divided into pN- and pN+ groups, and compared outcomes between patients who received no postoperative therapy and those who underwent postoperative RT/CCRT.

The status of margin is used to determine not only prognosis but also whether to perform adjuvant treatment such as radiation therapy, chemotherapy, or revision surgery. However, the relationship between the distance of margin and recurrence is controversial. PM is generally a poor prognostic factor [7-9]. And, an enough surgical margin of more than 5mm has been reported [10, 11]. Several investigators reported that increasing distance of the margin caused poor prognosis [12-14]. However, various cut-off points for the distance of the margin have been reported [9, 15-18]. In other studies, the distance of CM was variously reported as 2 mm [9], 5 mm [15, 16], 7 mm [17], and 10 mm [18]. In our study, we defined CM as < 5 mm, because finding a specific cut-off point was not a purpose of this study. In our results, negative margin was 83.3%, similar to that in other studies, in which the negative margin in OSCC varies between 53.5% and 85% [7, 19-21]. There was 12.1% of CM in this study within the reported range of 3% to 22%[12, 13, 22] of CM after surgery for OSCC.

Some investigators have indicated that the distance of margin was not a prognostic factor [13, 15, 23, 24]. However, many studies reported that a CM increased the risk of

local recurrence [7, 10, 19] and DSS [25]. CM may lead to local recurrence because of the remaining cancer cells or tumor satellites around the primary site [26]. Previous studies have reported that LC rates were 20-73.8 % for PM [27, 28] and 60-93 % for CM [15, 16, 23, 29]. In a systematic review, there was a stepwise improvement in oncologic outcomes as surgical margin categorically improved from PM to CM to clear margin [30]. Our results were similar to those of these previous studies [15, 16, 23, 27-30]. Moreover, on multivariate analysis in this study, CM or PM were independent predictors of DSS in the pN+ groups. It has been reported that PM is highly correlated to histological indicators of aggressive disease [7]. We also observed higher positive rates of LVSI in the CM (23.9%) and PM (29.0%) groups than in the negative margin (20.8%) groups in this study. CM or PM may be indicative of more aggressive tumor behavior. Some studies have shown that LVSI is a predictor of lymph node metastasis and prognosis [31, 32]. On the contrary, other studies demonstrated that LVSI did not associate with poor prognosis [33, 34]. The meta-analysis by Huang et al. showed that LVSI was associated with DSS [35]. They also suggested that LVSI has prognostic value in predicting the occurrence of lymph node metastasis in early-stage OSCC [35]. In the multivariate analysis of our study, LVSI was a significant risk factor of DSS in both pN- and pN+ groups.

The association between T classification and CM or PM is likely to reflect the problem that large tumors are a greater surgical challenge. In multivariate analysis of our study, higher T classification and CM or PM were significant risk factors of DSS in the pN- groups. The two risk factors may mainly affect LC. On the other hand, ENE and MLM were significant risk factors of DSS in only the pN+ groups. ENE and MLM may be associated with poor prognosis due to regional failure and distant metastasis, as in numerous other studies [4, 5, 36-40].

Acute and late adverse effects of postoperative RT are well known. Xerostomia, fibrosis, and trismus significantly decrease the quality of life for OSCC patients [41]. Osteoradionecrosis is a serious complication of postoperative RT, because of poor outcome

of conservative and radical treatment [42]. Furthermore, whether postoperative RT improves the outcome in OSCC patients with intermediate risk including CM is controversial [14, 17, 43-46]. Some studies reported that postoperative RT improved recurrence rates [45, 46], while other studies reported that the postoperative RT increased mortality (10-17%) and recurrence rates (10 %) [17, 43, 44]. Wong et al. demonstrated that locoregional control rates were better in the surgery-only group than in the combination therapy group [13]. Brown et al. found that survival rates were significantly better in the surgery-only group [43]. Therefore the decision to perform postoperative RT for patients with only CM as a risk factor may be difficult. There is little research focused on the effect of postoperative RT in pN- patients with CM because that population is so small [47]. Jang et al. demonstrated that adjuvant radiotherapy treatments did not significantly improve LC rate in early-stage oral cancer with CM [48]. Ch'ng et al. also suggested that surgery alone without postoperative adjuvant therapy offered acceptable LC in patients who had CM status as their only adverse feature [14]. Our data showed that the adjuvant therapy for patients with CM or PM provided no survival benefit, similar to previous studies.

This study had several limitations. First, the study was limited by its retrospective, non-matched design. Although multivariate analysis with patients divided into pN- and pN+ groups was performed to decrease the effect of confounding factors as far as possible, the possibility of selection bias could not be completely excluded. Second, the treatment protocols for RT/CCRT were not standardized because this was a retrospective study. Future research should involve a prospective cohort study with standardized treatment protocols and further exclude the bias in using propensity score matching analysis. If possible, a randomized setting should be applied for further investigation.

In conclusion, we analyzed the prognosis of patients with PM or CM divided into pN- and pN+ groups and identified significant multivariate relationships among risk factors of poor prognosis. Furthermore, we compared outcomes between patients who received no postoperative therapy and those who underwent postoperative RT/CCRT. The negative

margin was associated with a better LC rate than CM and PM. In multivariate analysis, higher T classification, LVSI, and older age were significant risk factor of DSS in the pN- groups. On the other hands, ENE MLM, and LVSI were significant risk factors of DSS in the pN+ groups. Our data failed to show a survival benefit of the adjuvant therapy for patients with CM or PM. However, there is generally a probable benefit of postoperative RT/CCRT in the prevention of disease recurrence. Therefore, these findings should be carefully considered because of the retrospective study design. Further, prospective randomized settings are necessary to demonstrate the usefulness of adjuvant treatment in patients with close margins.

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FIGURE CAPTIONS

FIGURE LEGENDS

Figure 1. The 3-year cumulative LC rates for the negative margin, CM, and PM pN- group were 93.8%, 83.0%, and 72.2%, respectively. Negative margin was associated with a better LC rate than CM and PM ($P < 0.05$). The 3-year cumulative DSS rates for the negative margin, CM, and PM of pN- group were 96.8%, 90.8%, and 91.4%, respectively. Negative margin was associated with a better DSS rate than CM ($P < 0.05$).

Figure 2. The 3-year cumulative LC rates for the negative margin, CM, and PM of pN+ group were 83.4%, 68.8% and 51.8%, respectively. Negative margin was associated with a better LC rate than CM and PM ($P < 0.05$). CM was associated with a better LC rate than PM ($P < 0.05$). The 3-year cumulative DSS rates for the negative margin, CM, and PM of pN+ group were 63.1%, 53.0%, and 48.2%, respectively. Negative margin was associated with a better DSS rate than PM ($P < 0.05$).

Figure 3. In pN- groups, the S only group was associated with a better LC rate than the S + RT/CCRT groups ($P < 0.05$).

Figure 4. In pN- groups, the S only group was associated with better RC, DM, and DSS rates than the S + RT/CCRT groups ($P < 0.05$).

Figure 5. In pN+ groups, there were no significant differences between S only and S + RT/CCRT groups.

Figure 6. In pN- groups, there were significant differences between S onlyl and S + RT/CCRT groups.

Table 1. Characteristics of patients in pN- and pN+ groups

Variables	Number of patients (%)	
	pN -	pN +
Number of patients	1488 (69.4)	657 (30.6)
Sex		
Male	824 (55.4)	393 (56.3)
Female	664 (44.6)	264 (43.7)
Age		
Range (Years)	15–99	15–96
Mean ± SD	66.4 ± 14.1	66.1 ± 14.1
Performance status		
0	1060 (71.2)	452 (68.8)
1	319 (21.4)	148 (22.5)
2	81 (5.4)	45 (6.9)
3	15 (1.0)	6 (0.9)
Unknown	13 (0.9)	6 (0.9)
Subsite		
Tongue	730 (49.1)	303 (46.1)
Buccal	147 (9.9)	62 (9.4)
Maxillary gingiva	184 (12.4)	79 (12.0)
Mandibular gingiva	306 (20.6)	150 (22.8)
Oral floor	121 (8.1)	63 (9.6)
T classification		
1	496 (33.3)	62 (9.4)
2	505 (33.9)	224 (34.1)
3	166 (11.2)	102 (15.5)
4a/b	321 (21.6)	269 (40.9)
Status of positive lymph metastasis		
ENE -	496 (33.3)	379 (57.7)
ENE +	-	278 (42.3)
Nonexcuted neck dissection on first surgery	992 (66.7)	0 (0)
Number of pathological lymph node metastases		
0	496 (33.3)	0 (0)
1	0 (0)	291 (44.3)
More than 2	0 (0)	366 (55.7)
Nonexcuted neck dissection on first surgery	992 (66.7)	0 (0)

Surgical margins		
Negative	1257 (84.5)	529 (80.5)
Close margins	171 (11.5)	88 (13.4)
Positive margins	60 (4.0)	40 (6.1)
Histological differentiation		
Well differentiated	859 (57.7)	306 (46.6)
Moderately differentiated	560 (37.6)	286 (43.5)
Poorly differentiated	51 (3.4)	63 (9.6)
Unknown	18 (1.2)	2 (0.3)
Lymphovascular space invasion		
No	863 (58.0)	211 (32.1)
Yes	216 (14.5)	246 (37.4)
Unknown	409 (27.5)	200 (30.4)
Neural Invasion		
No	1034 (69.5)	334 (50.8)
Yes	114 (7.7)	151 (23.0)
Unknown	340 (22.8)	172 (26.2)
Postoperative adjuvant therapy		
No	1443 (97.0)	391 (59.5)
Yes	45 (3.0)	266 (40.5)
Treatment outcome		
Survival	1320 (88.7)	362 (55.1)
Death of local failure	42 (2.8)	66 (10.0)
Death of regional failure	5 (0.3)	64 (9.7)
Death of distant metastasis	16 (1.1)	79 (12.0)
Death of other disease	83 (5.6)	50 (7.6)
Tumor-bearing survival	22 (1.5)	36 (5.5)

Table 2. Characteristics of patients according to LC and DSS in pN- and pN+ groups

Variables	pN -				pN +			
	3 year LC (%)	*P* value	3 year DSS (%)	*P* value	3 year LC (%)	*P* value	3 year DSS (%)	*P* value
Sex								
Male	93.0	0.006 *	96.2	0.293 *	80.8	0.066 *	59.1	0.562 *
Female	90.2		95.6		77.5		63.5	
Age								
≥ 70	88.0	< 0.001 *	94.2	< 0.001 *	74.0	< 0.001 *	59.7	0.768 *
≤ 69	94.8		97.4		83.7		61.5	
Performance status								
0, 1	92.2	0.005 *	96.0	0.367 *	80.3	0.154 *	62.0	0.178 *
≥ 2	81.4		93.8		69.7		42.9	
Subsite								
Tongue	95.8	< 0.001 *	98.0	< 0.001 *	82.6	0.020 *	56.9	0.596 *
Other	87.7		94.0		76.7		63.7	
T classification								
1, 2	94.8	< 0.001 *	98.2	0.001 *	86.2	< 0.001 *	64.4	0.003 *
3, 4a/b	85.4		91.3		74.2		57.7	
Status of positive lymph metastasis								
ENE -	-	-	-	-	81.2	0.153 *	71.5	< 0.001 *
ENE +	-		-		77.3		52.7	
Number of pathological lymph node metastases								
0, 1	-	-	-	-	82.7	0.104 *	70.8	< 0.001 *

More than 2	-		-		76.9		52.7	
Surgical margins								
Negative	93.8	< 0.001 *	96.8	< 0.001 *	83.4	< 0.001 *	63.1	0.055 *
Close or positive margins	80.1		91.0		63.4		51.6	
Histological differentiation								
Well or Moderately differentiated	92.1	0.011 *	96.2	0.028 *	80.2	0.287 *	62.9	0.011 *
Poorly differentiated	78.9		87.9		70.5		43.6	
Lymphovascular space invasion								
No	97.7	0.001 *	99.4	< 0.001 *	88.4	0.467 *	93.0	0.001 *
Yes	92.3		92.7		88.8		89.2	
Neural Invasion								
No	98.1	0.001 *	98.9	< 0.001 *	92.4	< 0.001 *	93.6	< 0.001 *
Yes	84.5		89.3		80.8		80.7	
Postoperative adjuvant therapy								
No	92.6	< 0.001 *	96.6	< 0.001 *	76.7	0.024 *	61.7	0.409 *
Yes	65.6		72.3		83.5		59.3	

Abbreviations: LC, local control rates; DSS, disease-specific survival rates ENE, extranodal extension

*: Log-rank test.

Table 3. Results of multivariate Cox proportional hazards analysis of predictors of disease specific survival in pN- patients

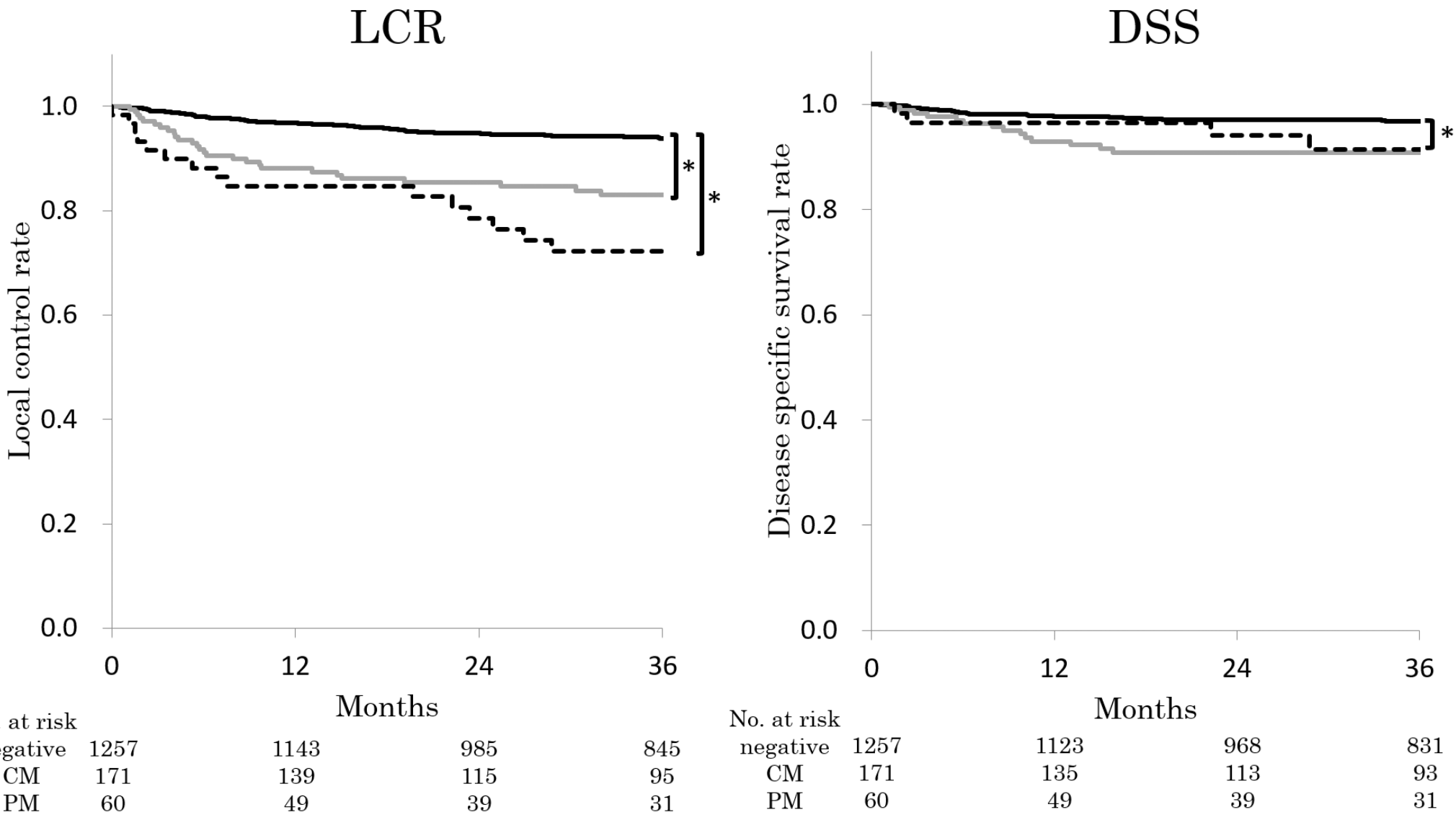
Variable	P value	Hazards ratio	95 % CI	
			Lower	Upper
Higher T classification (T3 and 4)	< 0.001	4.33	2.14	8.79
Lymphovascular space invasion	< 0.001	3.53	1.89	6.61
Older age (≥ 70 years)	< 0.001	3.90	1.90	7.98

CI: Confidence interval

Table 4. Results of multivariate Cox proportional hazards analysis of predictors of disease specific survival in pN+ patients

Variable	P value	Hazards ratio	95 % CI	
			Lower	Upper
Extra nodal extension	< 0.001	2.24	1.57	3.19
Lymphovascular space invasion	0.004	1.72	1.19	2.48
Close or positive margins	0.013	1.66	1.11	2.47
Multiple lymph node metastases	0.028	1.50	1.04	2.15

CI: Confidence interval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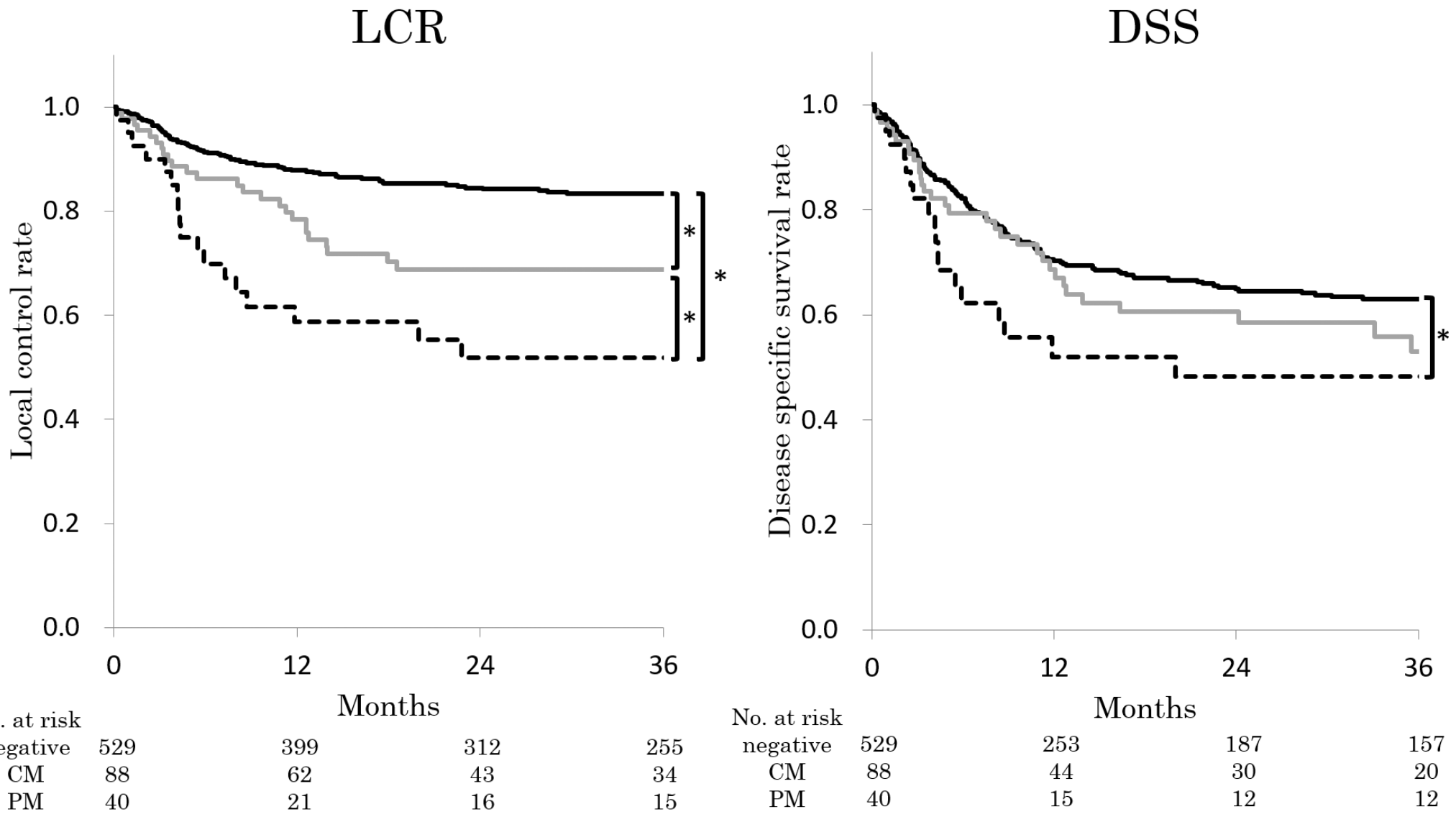
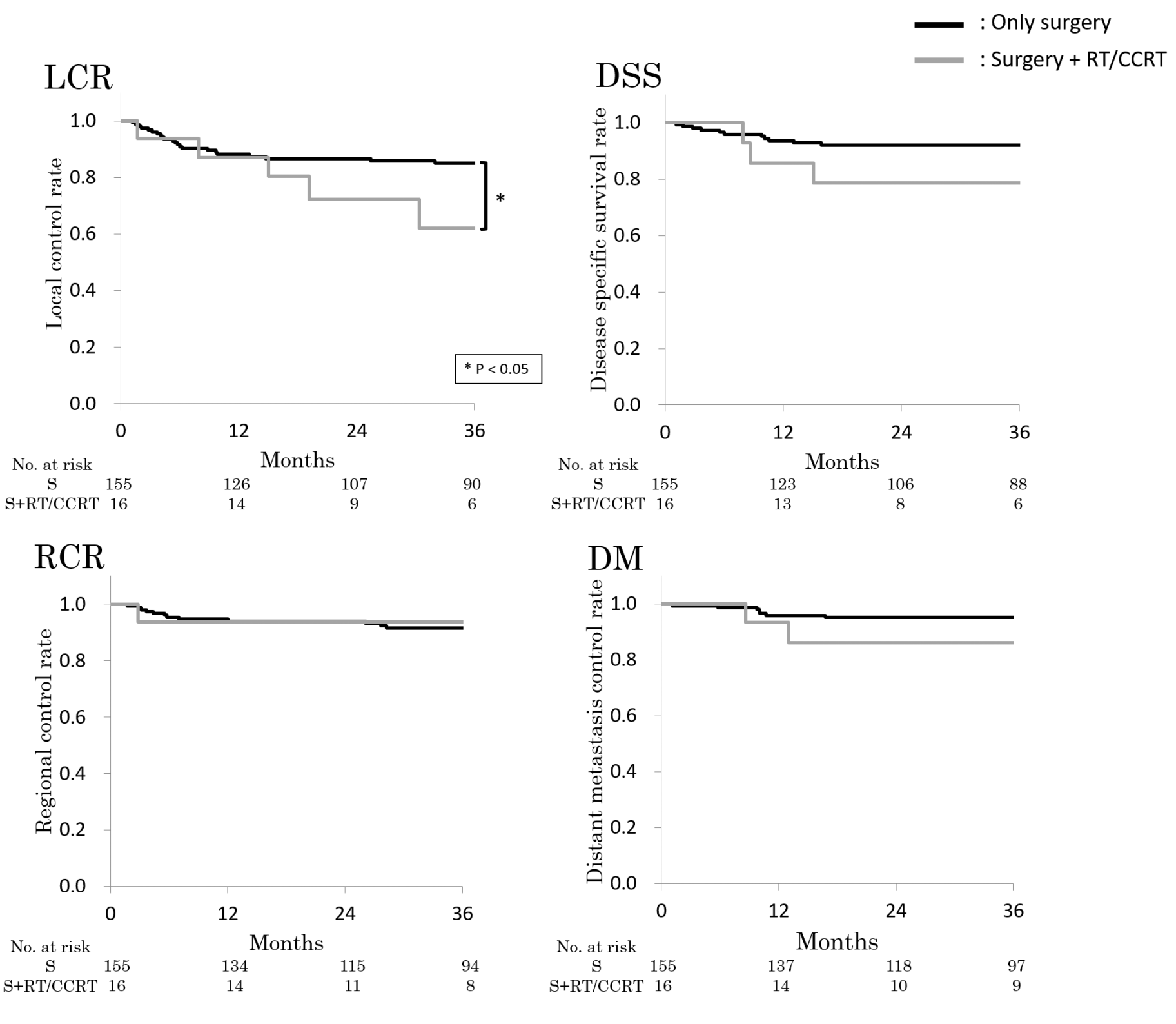
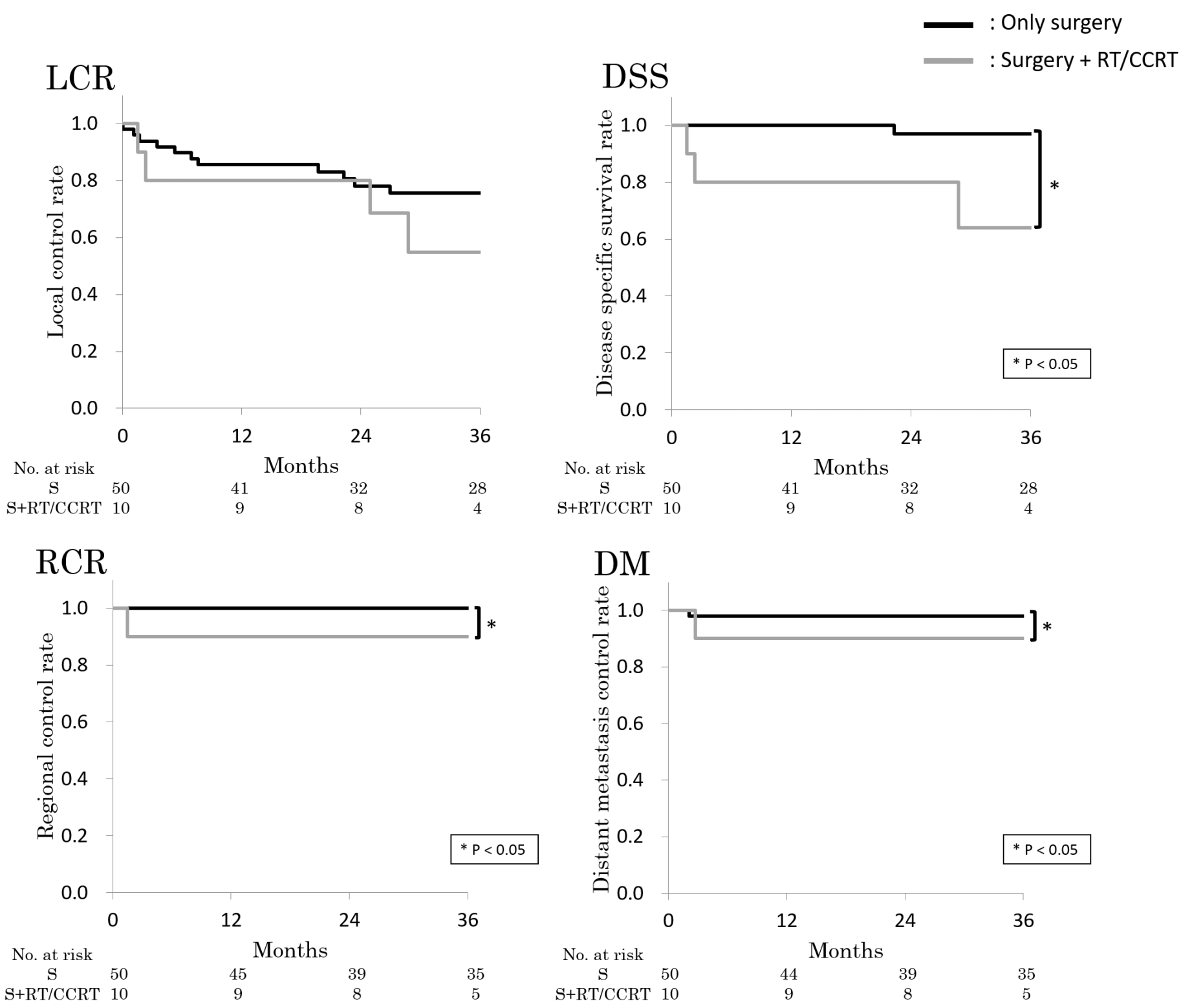
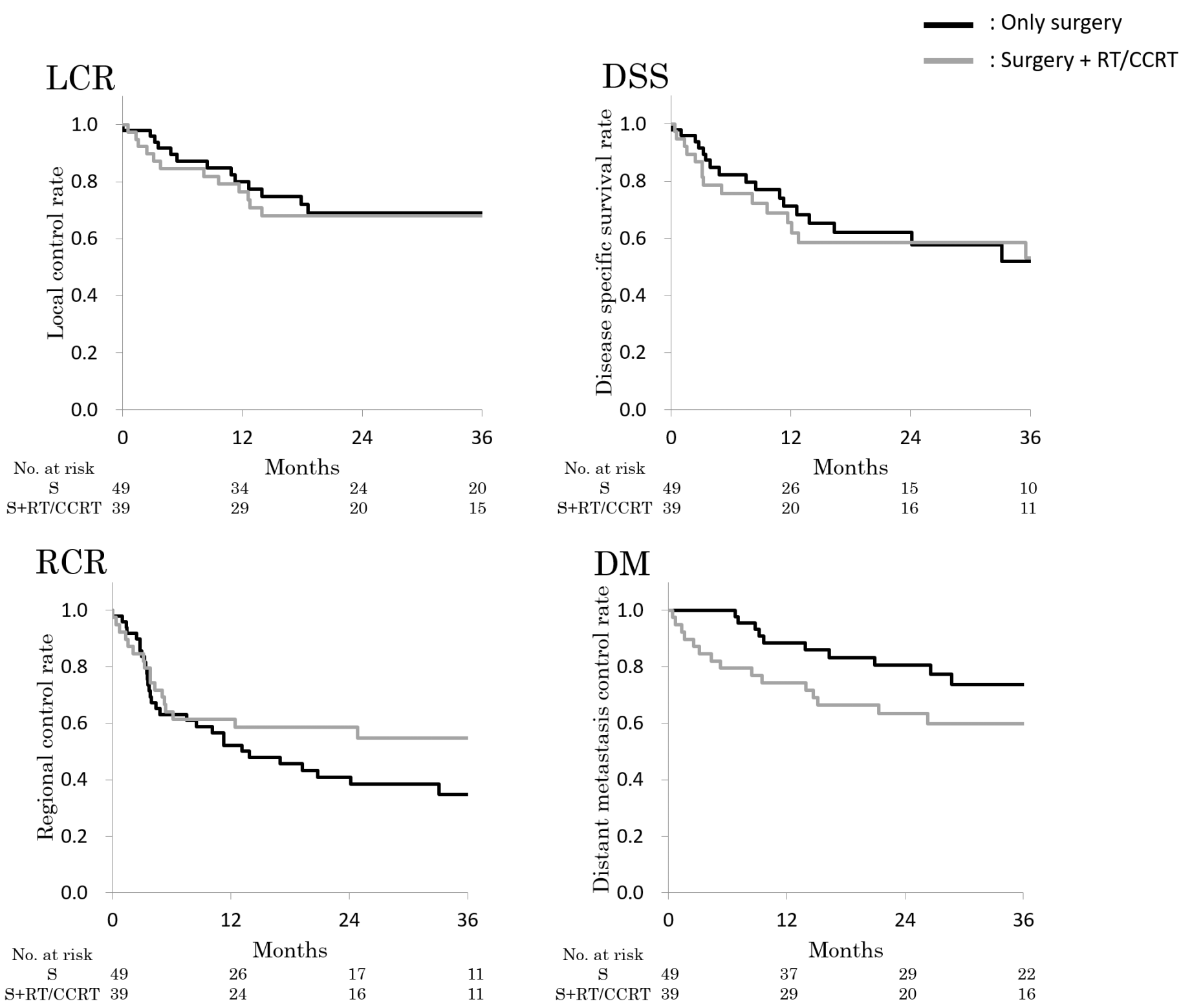
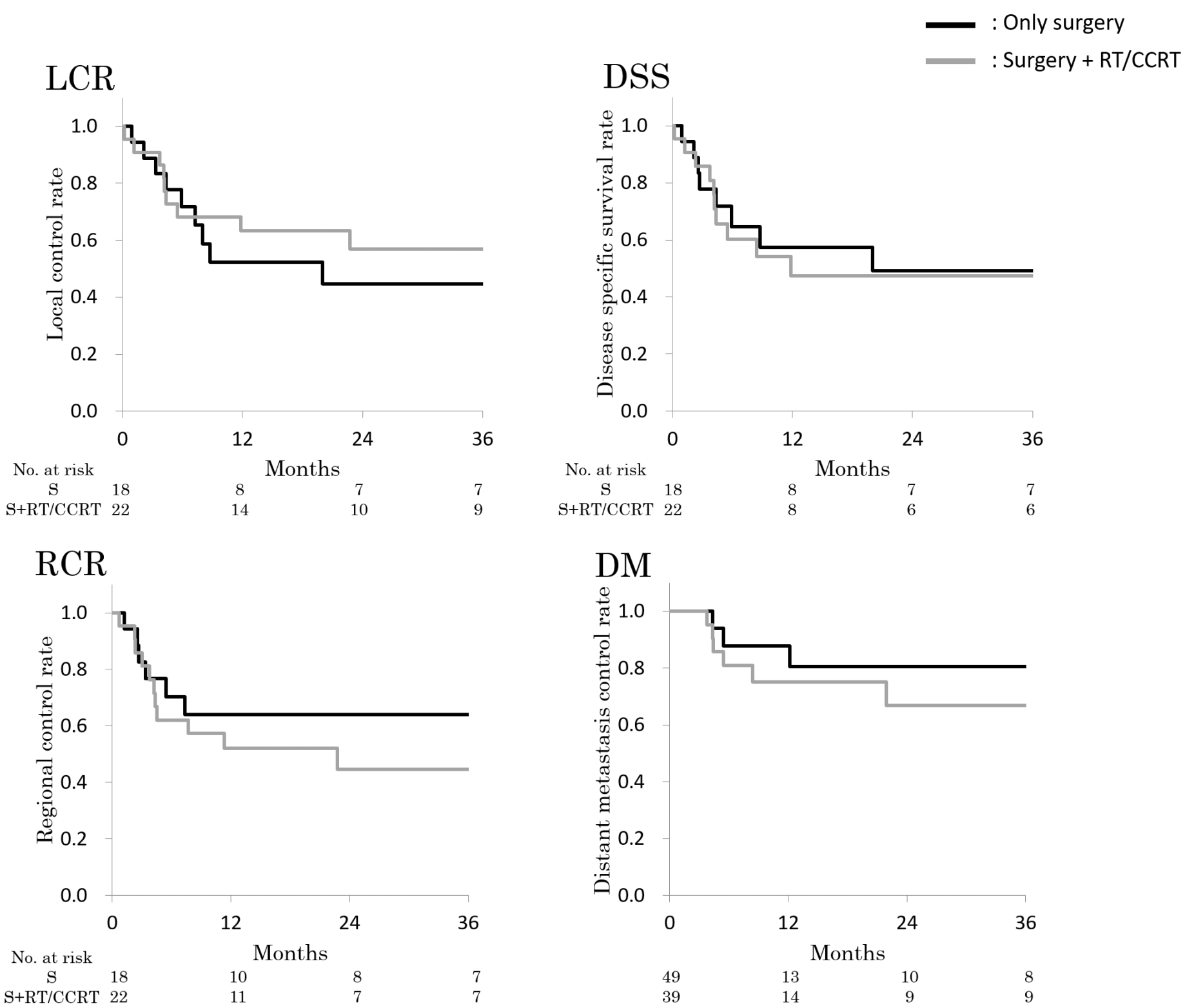
: Close margins
: Positive margins
LCR
Local control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
*
*
No. at risk
negative 1257 1143 985 845
CM 171 139 115 95
PM 60 49 39 31
DSS
Disease specific survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
*
No. at risk
negative 1257 1123 968 831
CM 171 135 113 93
PM 60 49 39 31


: Negative
: Close margins
: Positive margins
LCR
Local control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
*
*
*
No. at risk
negative 529 399 312 255
CM 88 62 43 34
PM 40 21 16 15
DSS
Disease specific survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
*
No. at risk
negative 529 253 187 157
CM 88 44 30 20
PM 40 15 12 12


: Only surgery
: Surgery + RT/CCRT
LCR
Local control rate
1.0
0.8
0.6
0.4
0.2
0.0
*
* P < 0.05
0
12
24
36
Months
No. at risk
S 155 126 107 90
S+RT/CCRT 16 14 9 6
DSS
Disease specific survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 155 123 106 88
S+RT/CCRT 16 13 8 6
RCR
Regional control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 155 134 115 94
S+RT/CCRT 16 14 11 8
DM
Distant metastasis control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 155 137 118 97
S+RT/CCRT 16 14 10 9


: Only surgery
: Surgery + RT/CCRT
LCR
Local control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 50 41 32 28
S+RT/CCRT 10 9 8 4
DSS
Disease specific survival rate
*
* P < 0.05
No. at risk
S 50 41 32 28
S+RT/CCRT 10 9 8 4
RCR
Regional control rate
*
* P < 0.05
No. at risk
S 50 45 39 35
S+RT/CCRT 10 9 8 5
DM
Distant metastasis control rate
*
* P < 0.05
No. at risk
S 50 44 39 35
S+RT/CCRT 10 9 8 5


: Only surgery
: Surgery + RT/CCRT
LCR
Local control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 49 34 24 20
S+RT/CCRT 39 29 20 15
DSS
Disease specific survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 49 26 15 10
S+RT/CCRT 39 20 16 11
RCR
Regional control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 49 26 17 11
S+RT/CCRT 39 24 16 11
DM
Distant metastasis control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 49 37 29 22
S+RT/CCRT 39 29 20 16


: Only surgery
: Surgery + RT/CCRT
LCR
Local control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 18 8 7 7
S+RT/CCRT 22 14 10 9
DSS
Disease specific survival rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 18 8 7 7
S+RT/CCRT 22 8 6 6
RCR
Regional control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
No. at risk
S 18 10 8 7
S+RT/CCRT 22 11 7 7
DM
Distant metastasis control rate
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
Months
49 13 10 8
39 14 9 9