Radiotherapy with or without Chemotherapy for Locally Advanced Head and Neck Cancer in Elderly Patients: Analysis of the Head and Neck Cancer Registry of Japan

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Abstract

Background: Whether concurrent chemotherapy with radiotherapy (CRT) is effective for elderly patients with head and neck cancer is a controversial topic. This study aimed to analyze the effectiveness of CRT vs. radiation therapy (RT) among elderly patients in Japan.

Methods: Data from the Head and Neck Cancer Registry of Japan were extracted and analyzed. Patients with locally advanced squamous cell carcinoma of the oropharynx, hypopharynx, or larynx who received definitive CRT or RT between 2011 and 2014 were included.

Results: CRT was administered to 78% of the 1,057 patients aged ≥70 years and 67% of the 555 patients aged ≥75 years. For the patients aged ≥75 years, the overall survival (OS) rate was significantly better in the CRT group than in the RT group ($P < 0.05$), while the progression-free survival (PFS) rate was not significantly different ($P > 0.05$). The add-on effect of CRT was significantly poor in elderly patients ($P < 0.05$), and it was not a significant

factor in the multivariate analysis for patients aged ≥75 years. After propensity score matching, there were no significant differences in the OS and PFS rates between the patients aged ≥70 years and those aged ≥75 years (all, $P > 0.05$).
Conclusion: Although aggressive CRT is administered to elderly patients in Japan, its effectiveness is uncertain. Further prospective randomized trials are needed to verify whether CRT is superior to RT alone for elderly patients.

Keywords: Head and neck cancer, Elderly, Chemoradiotherapy

Introduction

Chemoradiotherapy (CRT) is considered the standard of care among non-operative approaches for patients with locally advanced head and neck cancer. However, meta-analyses of prospective randomized trials have not consistently found improvements in survival with CRT compared to radiation therapy (RT) alone in elderly patients, especially those aged >70 years [1-3]. Retrospective analyses have shown conflicting conclusions regarding the superiority of CRT to RT for elderly patients [4, 5]. Due to a lack of evidence, the preference for CRT or RT alone for head and neck cancer in elderly patients varies widely among countries and institutions [6].

Japan currently has the highest rate of aging in the world [7]. Among head and neck cancer patients in Japan, the number of patients aged ≥70 years is increasing, accounting for almost half of all patients [8]. The global population is also rapidly aging. People from some Asian countries (e.g., the Republic of Korea, Singapore, China, and Thailand) are expected to age faster than those in Japan in the future [7]. Optimizing non-operative treatment for head and neck cancer in elderly patients is a new challenge facing Japan and an important worldwide issue. There is a lack of real-world data on CRT and RT for elderly patients with head and neck cancer in aging societies. This study aimed to investigate the effectiveness of CRT and definitive RT alone for elderly patients with head and neck cancer in Japan in terms of the prognosis using a head and neck cancer registry database.

Materials & Methods

Study design, database, and ethical statement

This retrospective study used a real-world data from the Head and Neck Cancer Registry of Japan, maintained by the Japan Society for Head and Neck Cancer (JSHNC) [8]. This is the largest real-world database of head and neck cancer patients in Japan and has been previously described in detail [9].

Data use was approved by the cancer registry committee of JSHNC (No. 2022-01). This study

was approved by the ethical review board of Hokkaido University Hospital (No. 023-0065). Informed consent was not required due to the retrospective nature of the study.

Patients' data and eligibility criteria

Five-year follow-up data registered in 2011, 2012, 2013, and 2014 were available at the time of conducting the study and extracted anonymously. The eligibility criteria were as follows: 1) primary site of oropharynx, hypopharynx, or larynx; 2) squamous cell carcinoma; 3) no metastasis; 4) stage III–IVB for p16-negative or unknown oropharyngeal, hypopharyngeal, or laryngeal cancer, or T4 or N3 for p16-positive oropharyngeal cancer as per the seventh edition of the Union for International Cancer Control Staging System; 4) definitive CRT or RT without surgery as initial treatment; and 5) age ≥70 years.

Main focus on the age of elderly patients

There are many studies on head and neck cancer in elderly patients, but the definitions of the term “elderly” used in these studies vary [10]. We focused on elderly patients aged ≥70 and also ≥75 years. In meta-analyses of prospective trials of head and neck cancer, no additional benefit of chemotherapy was demonstrated in elderly patients aged ≥70 years [2, 3]. In Japan, there are many active elderly people, and the Japan Gerontological Society and the Japan Geriatrics Society, after a three-year discussion based on various data on physical and psychological health, recommended that “old age” should be defined as age ≥75 years [11]. This is the definition widely used in Japan today. Since both definitions were considered clinically important and were the main focus of this study, statistical analyses were planned for all eligible patients aged ≥70 as well as those aged ≥75 years.

Statistical analysis

Student's t-test was used to compare continuous variables, and chi-square test was used to compare categorical variables between the two cohorts. Overall survival (OS) and progression-free survival (PFS) rates were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analyses using the Cox proportional hazards model were performed to determine the prognostic factors associated with OS or PFS. Patient variables included sex, age, smoking status, cancer site, stage, and performance status (PS). For the subgroup analyses, the hazard ratios for OS or PFS of CRT versus RT were calculated for the following subgroups: 70–74, 75–79, and ≥80 years, male and female; smoker and non-smoker status; disease originating in the hypopharynx, larynx, and oropharynx; stage III and IV disease; and PS of 0, 1, and ≥2. A test for interaction, using multivariable models including an interaction term (e.g., treatment vs. age) was conducted to check for statistically significant

differences between the subgroups [12]. For the propensity score matching analyses, patients in both groups were matched based on the factors used in the multivariate analysis. A caliper width of 0.2 standard deviations of the logit of the propensity score was used for patient selection. All *P* values were two-sided, with $P<0.05$ considered statistically significant. JMP Pro v17.0.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

The original data of 13,567 patients were obtained from the Head and Neck Cancer Registry of Japan. After excluding ineligible patients (Fig 1), a total of 1,057 patients were analyzed. The median follow-up period was 23.7 months for all patients and 46.0 months for censored patients. Of the 1,057 patients in the entire cohort, 828 (78%) received CRT. Of the 555 patients aged ≥75 years, 373 (67%) received CRT.

The characteristics of patients in the entire cohort are shown in Table 1. The CRT group was significantly younger, had more advanced stages of cancer, and had better PS scores than the RT group. There were significant differences in site, with a high prevalence of hypopharyngeal cancer among those who received CRT and a high prevalence of laryngeal cancer among those who received RT. The p16 status of most patients with oropharyngeal carcinoma was unknown (positive: 3, negative: 9, and unknown: 356).

Kaplan–Meier curves for OS and PFS are shown in Fig 2 for the entire cohort and for patients aged ≥75 years. Estimated OS and PFS rates are shown in Supplementary Table 1. For the entire cohort, the 5-year OS rate was 55.3% (95% confidence interval [CI]: 51.3–59.2) in the CRT group and 43.2% (95% CI: 35.5–51.3) in the RT group. The 5-year PFS rate was 43.3% (95% CI: 39.6–47.1) in the CRT group and 29.2% (22.7–36.7) in the RT group; both rates were significantly higher in the CRT group ($P < 0.05$). For patients aged ≥75 years, the 5-year OS rate was significantly higher in the CRT group at 49.7% (95% CI: 43.5–55.8) that that in the RT group at 38.7% (95% CI: 29.9–48.2; $P < 0.05$), while the 5-year PFS rate was 34.7% (95% CI: 29.4–40.4) in the CRT group and 24.5% (95% CI: 17.5–33.2) in the RT group, with no statistically significant difference ($P > 0.05$).

In the subgroup analysis (Fig 3), age showed a significant treatment interaction with the PFS rate (*P* for interaction < 0.05). No other factor showed treatment-by-subgroup interaction in the OS or PFS analysis. The multivariate analysis results for the OS and PFS rates are shown in Supplementary Table 2. CRT was a significant prognostic factor for OS and PFS among patients aged ≥70 years but not among those aged ≥75 years.

Patient characteristics before and after propensity score matching are shown in Supplementary Tables 3 and 4. The Kaplan–Meier curves for the OS and PFS rates among patients aged ≥70 and ≥75 years after propensity score matching are shown in Fig 4. The

95% CI for CRT and RT overlapped, and the differences in the OS and PFS rates between the groups were not statistically significant ($P > 0.05$).

Discussion

Over the next 3 decades, the number of elderly people worldwide is expected to more than double compared to that in 2019 and reach >1.5 billion by 2050 [7]. The aging rate in Japan has been high since 2005 and is currently the highest in the world [7]. The term elderly is generally used to refer to those aged ≥65 years; however, this age limit does not fit the aging society in Japan. Therefore, Japanese academic societies conducted a long discussion on the definition of the term elderly and examined various aspects of physical function, cognitive function, disease incidence, and mortality; they concluded that people aged >75 years at present were as young as those aged >65 years a decade or two ago [11]; hence, the term elderly is now used to refer to those aged ≥75 years in Japan. As the global population ages worldwide, studies that focus on those aged ≥70 or ≥75 years can have a major impact on real-world clinical practices.

The results of the present study showed aggressive use of CRT in Japan, similar to the situation in the U.S. [4,5] as opposed to that in European countries [6]. In the analyses based on patients' characteristics, there was no significant difference in the PFS rate between CRT and RT use among patients aged ≥75 years. In the subgroup analysis, age showed a significant treatment interaction with the PFS rate (the effect was poorer in elderly patients), and in the multivariate analysis, CRT was not a significant factor for those aged ≥75 years. When patients' characteristics were matched, there were no significant differences in the OS and PFS rates among those aged ≥70 years or those aged ≥75 years. In Japan, aggressive CRT is administered to elderly as well as non-elderly patients because it is believed to be more effective than RT alone. However, the results of the present study are consistent with the results of a meta-analysis of prospective trials and raise the question of the additional effects of chemotherapy and RT in elderly patients.

The lack of the add-on effect of chemotherapy can be attributed to the fact that it is not being effectively used for elderly patients. The standard 100 mg/m^2 dose of cisplatin given in three sessions is often difficult to administer to elderly patients [13, 14]. Other doses of cisplatin may be administered, or other chemotherapies may be used. Other doses of cisplatin were reported to be useful in a phase III prospective study that excluded elderly patients [15]. Carboplatin is often administered to elderly patients [6], but its efficacy has not been proven in phase III prospective trials. Cetuximab does not have fewer side effects than cisplatin [16, 17], and it may be less effective in older patients [18, 19]. However, the database we used did not register the dose or kind of chemotherapy, and there is no evidence to support this

possibility.

The best age definition to use when studying the add-on effect of chemotherapy is a very interesting topic. In addition to age, other factors such as PS, renal function, comorbidities, cognitive function, social support, etc., are probably relevant, and detailed data analyses are needed. It is difficult to analyze these aspects using data from a national database. We examined the data using only two important age definitions in a predetermined manner. In future prospective clinical trials of elderly patients with head and neck cancer, detailed data should be obtained and analyzed from this perspective.

This study had a few limitations. First, there was little information on p16 status in the patients with oropharyngeal carcinoma. In Japan, p16 status was rarely tested between 2011 and 2014. In this analysis, patients with stage III (T3N0, T1–3N1), stage IVA (T4N0–2), and stage IVB (anyTN3) disease were considered eligible if the p16 status was unknown. Therefore, it is possible that some patients with p16-positive were included in this study. These patients were more favorable prognostics and generated uncertainty in the results and the interpretation, which weakens the conclusions of this study. However, its effect on comparisons between the groups might have been diluted since an approximately equal number of oropharyngeal patients were randomly assigned to both groups after propensity score matching. In addition, the dose and type of chemotherapy were not known. Furthermore, although propensity score matching was performed, it fundamentally compared groups with significant bias in patient background.

CRT for head and neck cancer is more toxic than RT alone. Standard CRT with cisplatin causes late adverse events, such as dysphagia and treatment-related death after treatment. A prospective randomized trial suggested that the drawbacks mitigated the benefits of chemotherapy and could make survival worse than RT alone [20]. Prospective trials are needed to determine whether CRT is beneficial for elderly patients.

Conclusion

Aggressive CRT is administered to elderly patients in Japan, but its effectiveness is uncertain, warranting further exploration. Prospective randomized trials are needed to determine whether CRT is superior to RT alone for elderly patients.

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Figure legends

Fig 1
Flowchart of patient selection
Abbreviations: SqCC = squamous cell carcinoma, UICC = The Union for International Cancer Control.

Fig 2
Kaplan–Meier curves including 95% confidence interval for OS (A) and PFS (B) of those aged ≥70 years and OS (C) and PFS (D) of those aged ≥75 years. Red = CRT, Green = RT.
Abbreviations: CRT = chemoradiotherapy, RT = radiation therapy alone.

Fig 3
Subgroup analysis of treatment interaction for OS (A) and PFS (B)
Abbreviations: CRT = chemoradiotherapy, PS = performance status, RT = radiation therapy alone.

Fig 4
Kaplan–Meier curves including 95% confidence interval after propensity score matching for OS (A) and PFS (B) of patients aged ≥70 years and OS (C) and PFS (D) of those aged ≥75 years. Red = CRT, Green = RT.
Abbreviations: CRT = chemoradiotherapy, RT = radiation therapy alone.

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Author contributions
KY: conceptualization and design; development of the methodology; acquisition and analysis of the data; and writing, review, and revision of the article. YU: development of the methodology and review and revision of the article. SK: review and revision of the article. JT: review and revision of the article. DK: ethics review; acquisition and processing of data; and review of the article. MK: acquisition of data and review of the article. KN: review and revision of the article. TM: review and revision of the article. FK: analysis of the data and review and revision of the article. YF: analysis of the data and review and revision of the article. YS: review and revision of the article. KK: review and revision of the article. SY: ethics review; and review of the article. KN: ethics review and review of the article. AH: review and revision of the article. HA: review and revision of the article; and funding acquisition.

Data availability
The data generated in this study are available in the article.

Declarations

Conflict of interest: KK is an employee of an institute of Hitachi Ltd. and currently works for Hokkaido University under a secondary agreement, but KK declares that this research has no relationship with Hitachi Ltd.

Table 1: Characteristics of the patients

	CRT	RT	*P*-value
N	828	229	
Age (mean ± SD)	74.8 ± 4.2	79.6 ± 5.4	<0.0001
70–74	455 (55%)	47 (21%)	
≥75	373 (45%)	182 (79%)	
Sex			0.6796
Male	752 (91%)	210 (92%)	
Female	76 (9%)	19 (8%)	
Smoking status			0.7481
Smoker	549 (66%)	147 (64%)	
Non-smoker	101 (12%)	32 (14%)	
Unknown	178 (22%)	50 (22%)	
Site			<0.0001
Hypopharynx	373 (45%)	66 (29%)	
Larynx	171 (21%)	79 (35%)	
Oropharynx	284 (34%)	84 (37%)	
Stage			<0.0001
3	282 (34%)	126 (55%)	
4	546 (66%)	103 (45%)	
PS			0.0016
0	510 (70%)	132 (62%)	
1	161 (22%)	46 (22%)	
≥2	36 (4%)	25 (11%)	
Unknown	25 (3%)	10 (5%)	

Abbreviations: CRT = chemoradiation therapy, PS = performance status, RT = radiation therapy, SD = standard deviation

Fig 1

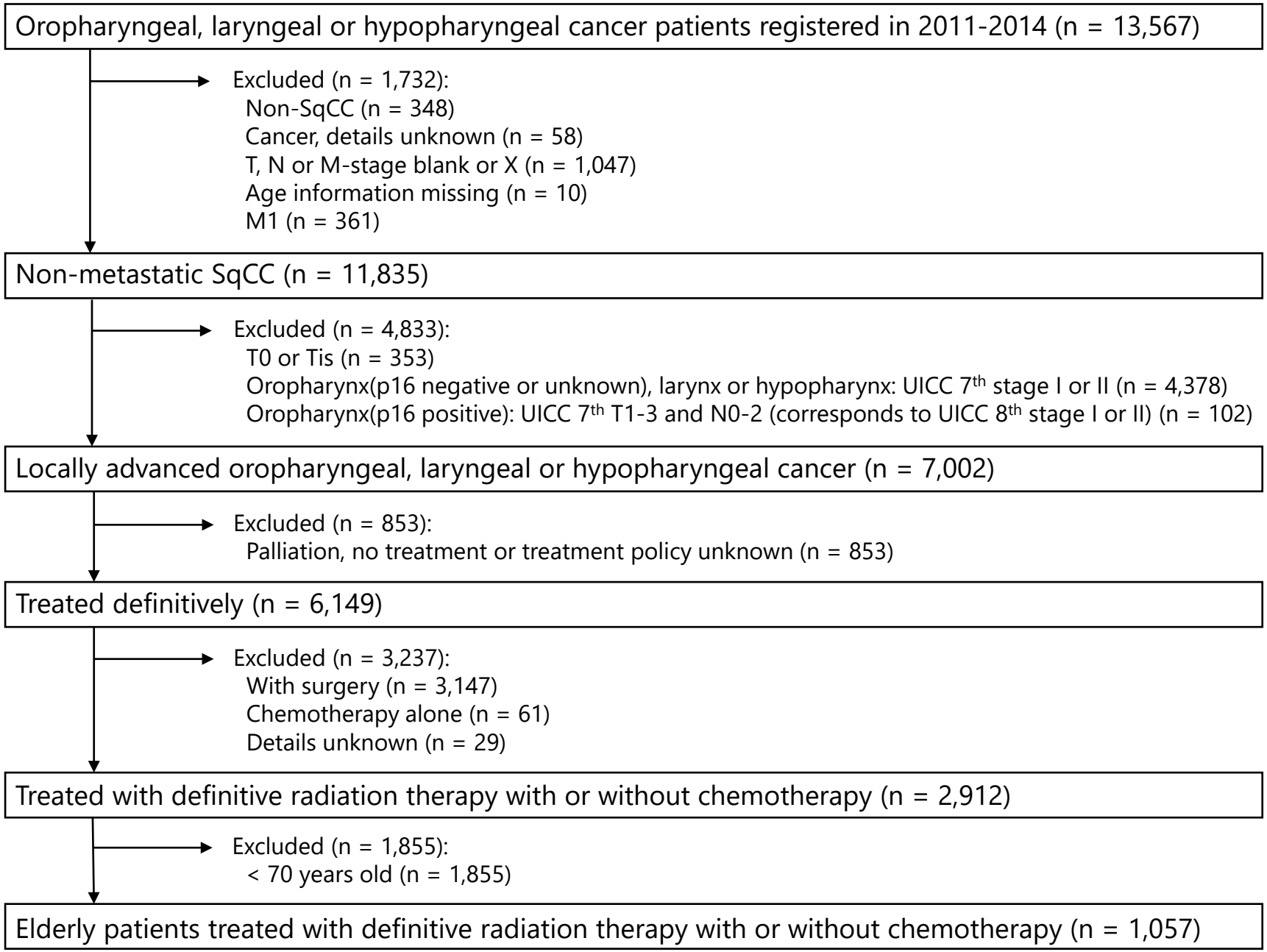

Oropharyngeal, laryngeal or hypopharyngeal cancer patients registered in 2011-2014 (n = 13,567)
Excluded (n = 1,732):
Non-SqCC (n = 348)
Cancer, details unknown (n = 58)
T, N or M-stage blank or X (n = 1,047)
Age information missing (n = 10)
M1 (n = 361)
Non-metastatic SqCC (n = 11,835)
Excluded (n = 4,833):
T0 or Tis (n = 353)
Oropharynx(p16 negative or unknown), larynx or hypopharynx: UICC 7th stage I or II (n = 4,378)
Oropharynx(p16 positive): UICC 7th T1-3 and N0-2 (corresponds to UICC 8th stage I or II) (n = 102)
Locally advanced oropharyngeal, laryngeal or hypopharyngeal cancer (n = 7,002)
Excluded (n = 853):
Palliation, no treatment or treatment policy unknown (n = 853)
Treated definitively (n = 6,149)
Excluded (n = 3,237):
With surgery (n = 3,147)
Chemotherapy alone (n = 61)
Details unknown (n = 29)
Treated with definitive radiation therapy with or without chemotherapy (n = 2,912)
Excluded (n = 1,855):
< 70 years old (n = 1,855)
Elderly patients treated with definitive radiation therapy with or without chemotherapy (n = 1,057)

Fig 2

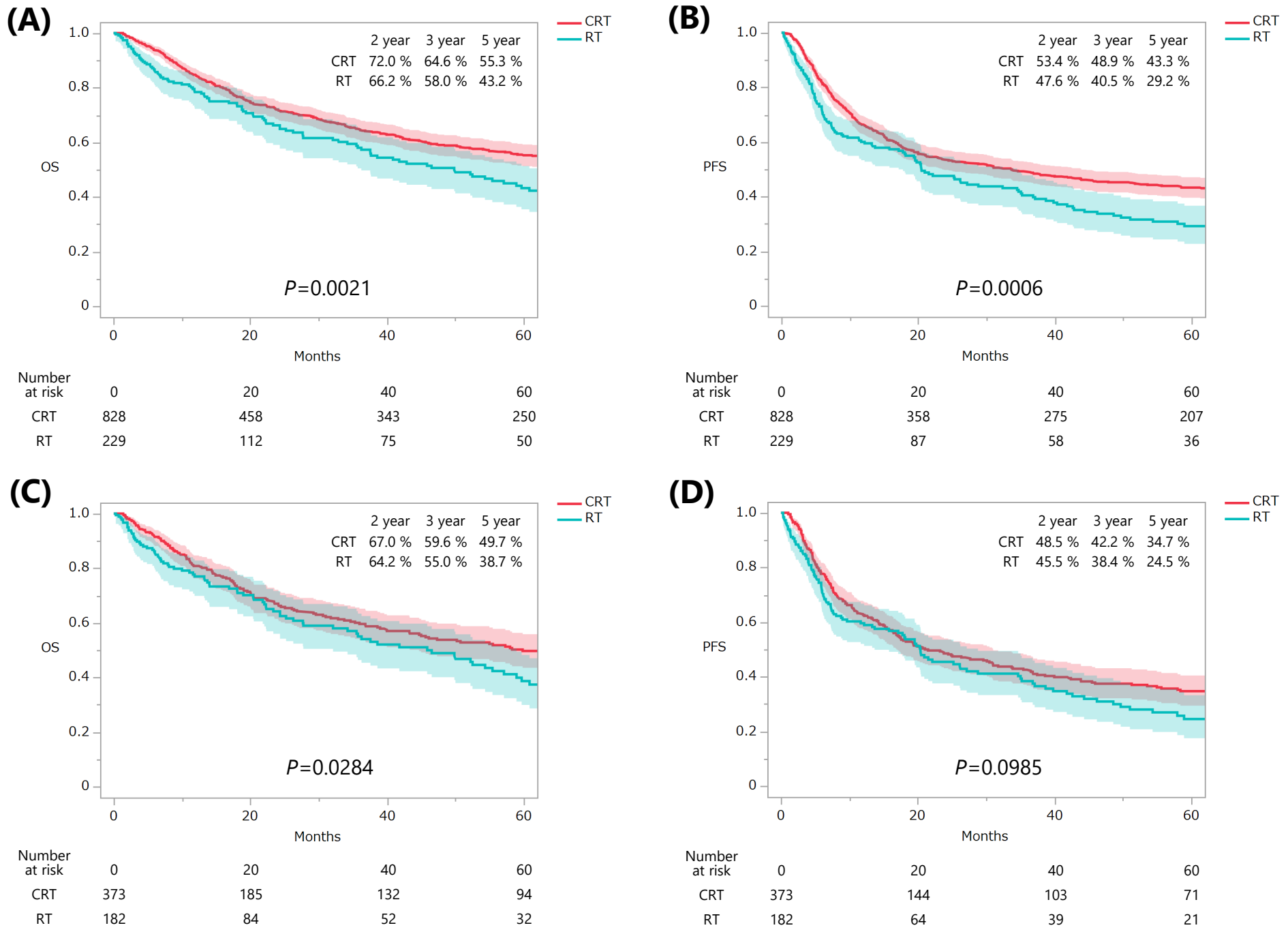
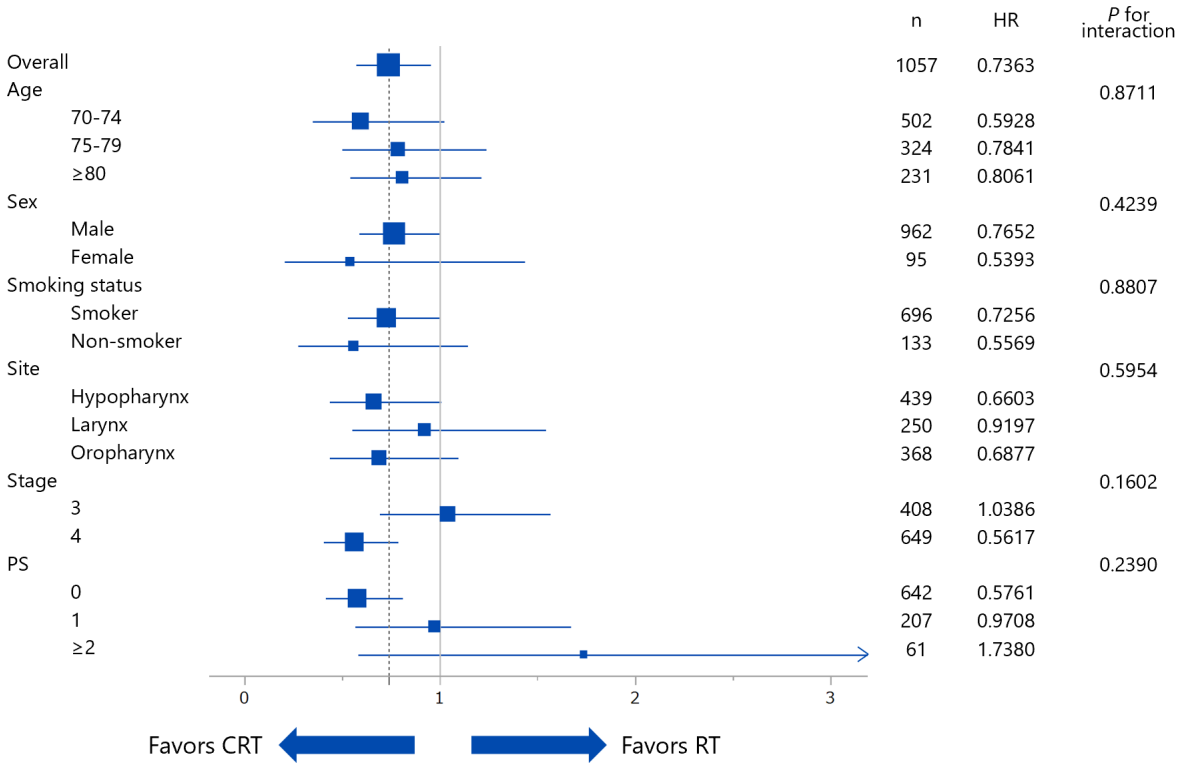

(A)
CRT
RT
2 year 3 year 5 year
CRT 72.0 % 64.6 % 55.3 %
RT 66.2 % 58.0 % 43.2 %
OS
P=0.0021
Months
Number at risk 0 20 40 60
CRT 828 458 343 250
RT 229 112 75 50
(B)
CRT
RT
2 year 3 year 5 year
CRT 53.4 % 48.9 % 43.3 %
RT 47.6 % 40.5 % 29.2 %
PFS
P=0.0006
Months
Number at risk 0 20 40 60
CRT 828 358 275 207
RT 229 87 58 36
(C)
CRT
RT
2 year 3 year 5 year
CRT 67.0 % 59.6 % 49.7 %
RT 64.2 % 55.0 % 38.7 %
OS
P=0.0284
Months
Number at risk 0 20 40 60
CRT 373 185 132 94
RT 182 84 52 32
(D)
CRT
RT
2 year 3 year 5 year
CRT 48.5 % 42.2 % 34.7 %
RT 45.5 % 38.4 % 24.5 %
PFS
P=0.0985
Months
Number at risk 0 20 40 60
CRT 373 144 103 71
RT 182 64 39 21

Fig 3

(A)


n
HR
P for interaction
Overall 1057 0.7363
Age 0.8711
70-74 502 0.5928
75-79 324 0.7841
≥80 231 0.8061
Sex 0.4239
Male 962 0.7652
Female 95 0.5393
Smoking status 0.8807
Smoker 696 0.7256
Non-smoker 133 0.5569
Site 0.5954
Hypopharynx 439 0.6603
Larynx 250 0.9197
Oropharynx 368 0.6877
Stage 0.1602
3 408 1.0386
4 649 0.5617
PS 0.2390
0 642 0.5761
1 207 0.9708
≥2 61 1.7380
0
1
2
3
Favors CRT
Favors RT

(B)

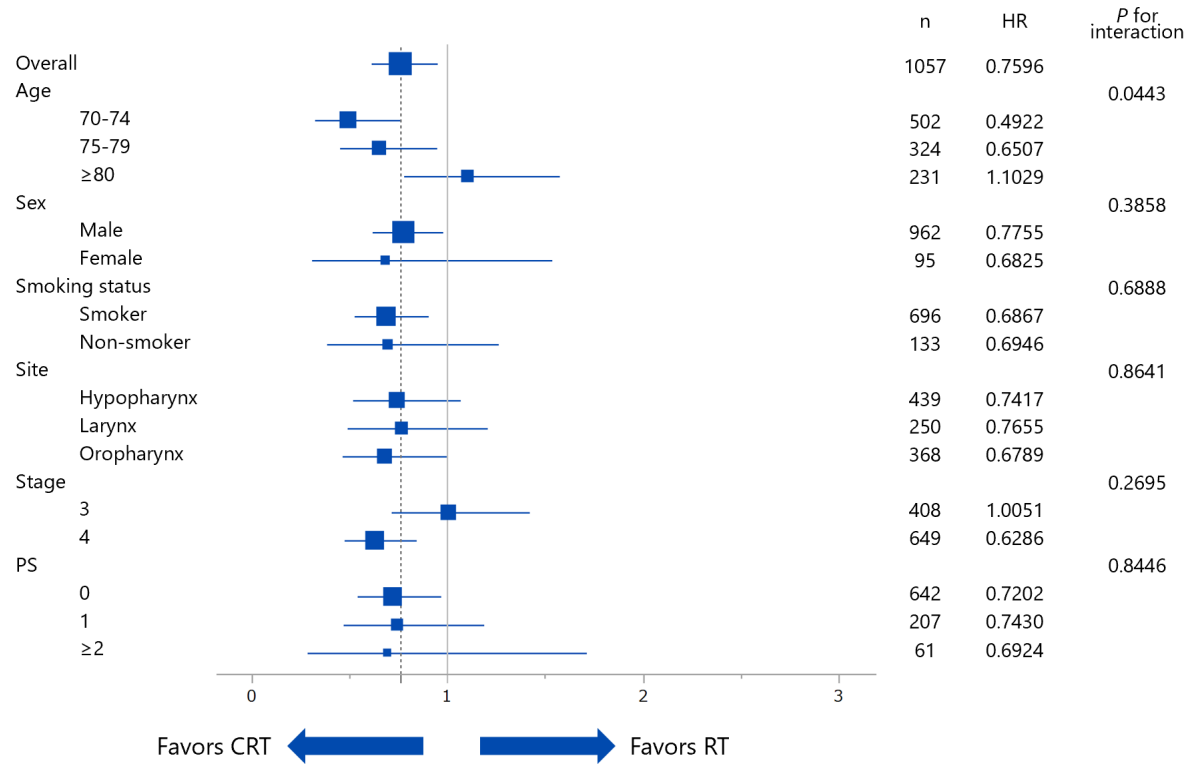
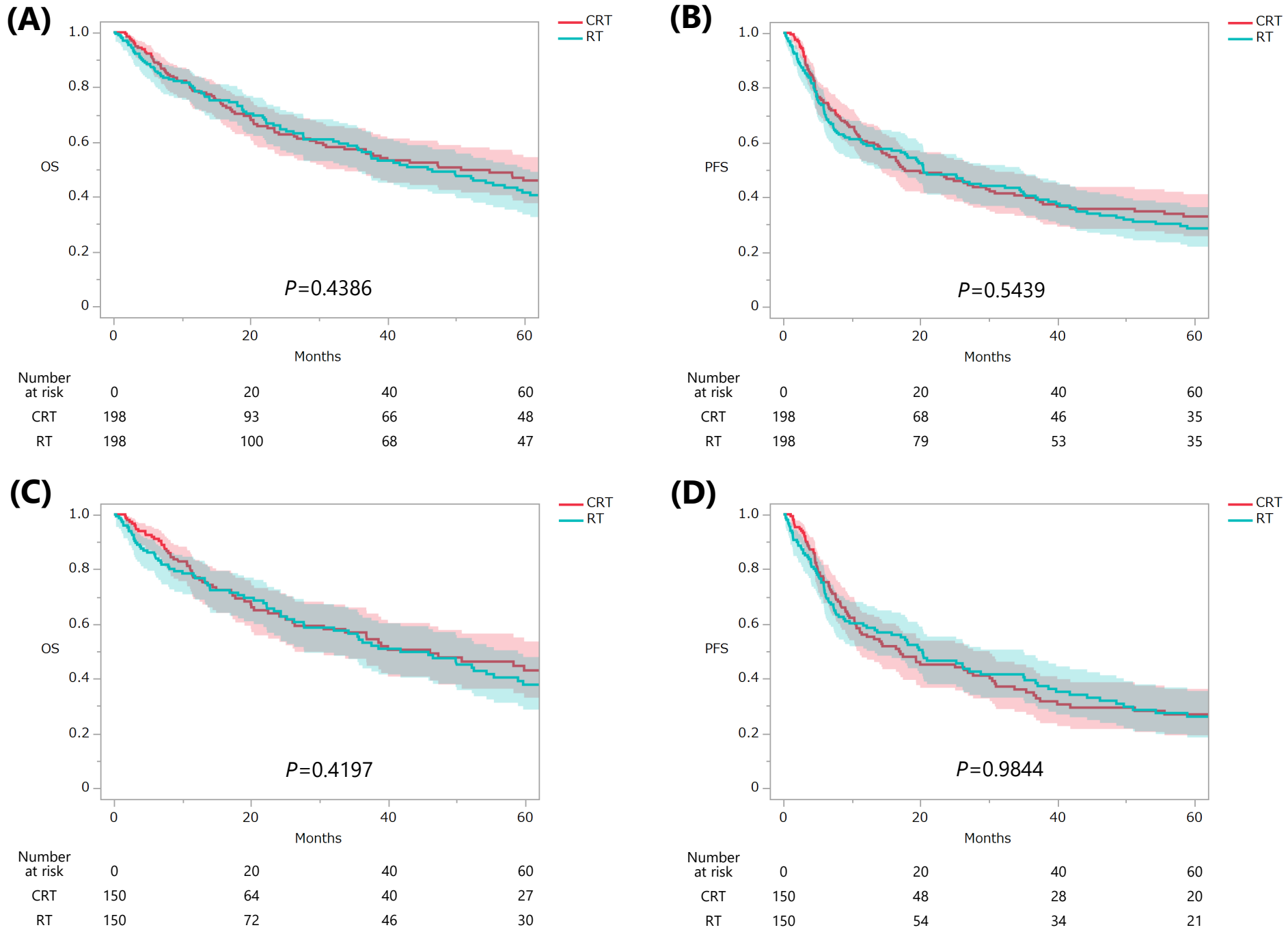

n
HR
P for interaction
Overall 1057 0.7596
Age 0.0443
70-74 502 0.4922
75-79 324 0.6507
≥80 231 1.1029
Sex 0.3858
Male 962 0.7755
Female 95 0.6825
Smoking status 0.6888
Smoker 696 0.6867
Non-smoker 133 0.6946
Site 0.8641
Hypopharynx 439 0.7417
Larynx 250 0.7655
Oropharynx 368 0.6789
Stage 0.2695
3 408 1.0051
4 649 0.6286
PS 0.8446
0 642 0.7202
1 207 0.7430
≥2 61 0.6924
0
1
2
3
Favors CRT
Favors RT

Fig 4


(A)
CRT
RT
1.0
0.8
0.6
0.4
0.2
0
OS
P=0.4386
0
20
40
60
Months
Number at risk
CRT 198 93 66 48
RT 198 100 68 47
(B)
CRT
RT
PFS
P=0.5439
Months
Number at risk
CRT 198 68 46 35
RT 198 79 53 35
(C)
CRT
RT
OS
P=0.4197
Months
Number at risk
CRT 150 64 40 27
RT 150 72 46 30
(D)
CRT
RT
PFS
P=0.9844
Months
Number at risk
CRT 150 48 28 20
RT 150 54 34 21