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Long-term oncological and functional outcomes of induction chemotherapy followed by (chemo)radiotherapy vs definitive chemoradiotherapy vs surgery-based therapy in locally advanced stage III/IV hypopharyngeal cancer: Multicenter review of 266 cases

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ABSTRACT

Objective: The aim of this study was to evaluate the treatment outcomes for stage III/IV locally advanced hypopharyngeal squamous cell carcinoma (SCC), comparing induction chemotherapy followed by (chemo)radiotherapy (ICT), definitive chemoradiotherapy (CRT) and surgery-based therapy (SRT). *Subjects and Methods:* Two hundred sixty-six patients with stage III/IV locally advanced hypopharyngeal squamous cell carcinoma (SCC) who underwent ICT (n = 74), CRT (n = 53) or SRT (n = 139) from 1997 through 2014 at the Seoul National University Hospital (n = 127) and the Hallym University Medical Center (n = 139) were enrolled in the study. All surgical procedures in the SRT group were performed by a single surgeon to eliminate surgeon bias. *Results:* The 5-year disease-free survival (DFS) and overall survival (OS) of all patients (n = 266) were 59.4% and 44%, respectively. The 5-year DFS rates after salvage treatment were 52.7% for ICT, 52.8% for CRT and 65.5% for SRT ($p = 0.194$). The OS rates were 44.6% for ICT, 39.6% for CRT and 45.3% for SRT group ($p = 0.106$). The salvage rates were 12.5% for ICT, 15.6% for CRT and 3.8% for SRT group. The final laryngeal preservation rate was significantly lower in the SRT group (44.6%) than in the ICT (71.6%) or CRT (71.7%) groups. All major postoperative complications were significantly higher in the salvage surgery group. *Conclusion:* Treatment outcomes in the ICT and CRT groups were comparable to that of the SRT group for stage III/IV hypopharyngeal SCC. However, the relatively low chance of cure and high risk of complications should be taken into account when considering salvage surgery.

Introduction

Squamous cell carcinoma (SCC) of hypopharynx is a highly aggressive cancer that is diagnosed at an advanced stage in most cases; therefore, the prognosis is poor and the survival rate is low. Given the complexity of these tumors, their surrounding structures, and the frequent comorbidities, a multidisciplinary treatment approach should be applied to achieve the best oncological outcomes and to improve functional results [1,2].

Treatment options for early-stage disease include both surgery-based and radiotherapy (RT)-based approaches that preserve the organ and function [2]. Advanced tumors of the hypopharynx requiring pharyngectomy with total laryngectomy (over T3) are often managed by induction chemotherapy followed by definitive (chemo)radiation or

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surgery, depending on the response of the induction chemotherapy or multi-modality approaches. However, there have been no clear guidelines specific for hypopharyngeal cancer. Most studies of laryngeal preservation were from laryngeal cancer or mixed head and neck cancer trials. Although a few studies reported treatment results of hypopharyngeal SCC, they included a mixture of early stage cancers and advanced unresectable cancers [3]. The aim of this study was to evaluate the treatment outcomes for locally advanced stage III/IV hypopharyngeal SCC, comparing induction chemotherapy followed by (chemo) radiotherapy (ICT), definite chemoradiotherapy (CRT) and surgery-based therapy (SRT).

Materials and methods

Patient population

The study protocol was approved by the Institutional Review Board of SNUH (approval number: 1608-025-782). Three hundred sixty-seven patients with resectable stage III/IV hypopharyngeal SCC who underwent curative treatment at the Seoul National University Hospital (SNUH, n = 217) and the Hallym University Medical Center (HUMC, n = 150) from 1997 through 2014 were enrolled in the study. Patients with stage I/II (n = 52) and those who underwent SRT at SNUH (n = 48, to analyze only one surgeon's data in the SRT group) or induction chemotherapy followed by surgery (n = 1, to clarify the surgical vs. nonsurgical arms) were excluded. Consequently, a total of 266 patients with stage III/IV hypopharyngeal SCC who were treated with ICT (n = 74), CRT (n = 53) or SRT (n = 139) were retrospectively analyzed. Induction chemotherapy was followed by definitive RT (n = 20) or CRT (n = 54) according to the response of chemotherapy and the patient's choice (Fig. 1).

The detailed pretreatment assessment of the extent of the primary tumor and second primary neoplasms included an endoscopic examination in the outpatient clinic and the operating room, esophagogastroduodenoscopy, ultrasound (with or without fine needle aspiration biopsy under ultrasound guidance), CT/MRI and positron emission tomography (PET). Patients were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system. While the patients treated with ICT or CRT were staged clinically, pathologic stage was used for the SRT group.

Table 1
Clinicopathological factors influencing disease-free survival and overall survival of 266 patients with hypopharyngeal squamous cell carcinoma. Values indicated by '*' are statistically significant. *Abbreviations:* DFS = disease-free survival; OS = overall survival; PC = postcricoid; PPW = posterior pharyngeal wall; ICT = induction chemotherapy followed by (chemo)radiotherapy; CRT = chemoradiotherapy, SRT = surgery-based therapy.

Variable	Variable	DFS		Variable	OS	
		5-yr DFS	p-value		5-yr OS	*p*-value
Age (yr)			0.232			0.057
≤60	29/77	62.3%		39/77	49.4%	
> 60	79/189	58.2%		110/189	41.8%	
Sex			0.855			0.941
Male	102/249	59.0%		141/249	43.4%	
Female	6/17	64.7%		8/17	52.9%	
Subsite			0.025*			0.009*
PC/PPW	26/50	48%		34/50	32%	
PS	82/216	62.0%		115/216	46.8%	
T stage			0.035*			0.017*
T1-2	38/112	66.1%		54/112	51.8%	
T3-4	70/154	54.5%		95/154	38.3%	
N stage			0.074			0.578
N0-1	20/63	68.3%		34/63	46%	
N2-3	88/203	56.7%		115/203	43.3%	
Treatment			0.194			0.106
ICT	35/74	52.7%		41/74	44.6%	
CRT	25/53	52.8%		32/53	39.6%	
SRT	48/139	65.5%		76/139	45.3%	

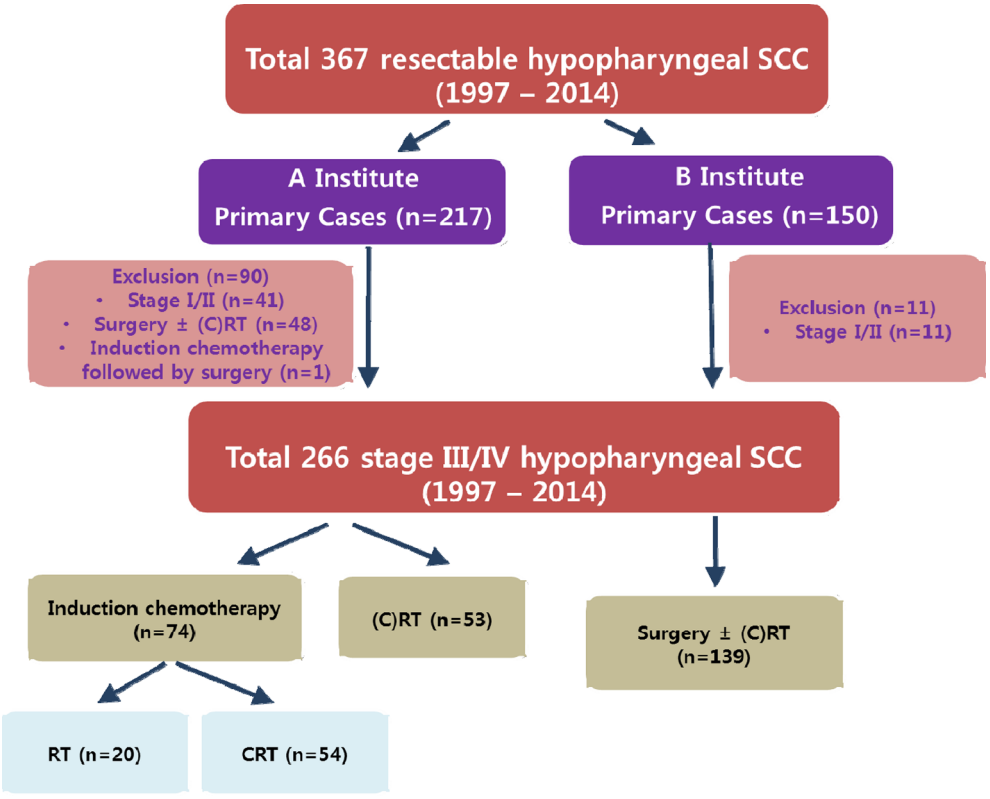


Fig. 1. Schema showing the included patient population. Three hundred sixty-seven patients with resectable hypopharyngeal SCC who underwent curative treatment at the Seoul National University Hospital (SNUH, n = 217) and the Hallym University Medical Center (HUMC, n = 150) from 1997 through 2014 were enrolled in the study. Patients with stage I/II (n = 52) and who underwent SRT in SNUH (n = 48, to analyze only one surgeon's data in SRT group or induction chemotherapy followed by surgery (n = 1, to clarify the surgical vs. nonsurgical arms), were excluded. Consequently, a total of 266 patients with stage III/IV hypopharyngeal squamous cell carcinoma treated with induction chemotherapy (n = 74), definitive chemoradiotherapy (n = 53) and surgery-based treatment (n = 139) were retrospectively analyzed in this study. Abbreviations: SCC = Squamous cell carcinoma; CRT = definitive chemoradiotherapy; SRT = surgery-based therapy; RT = radiotherapy.

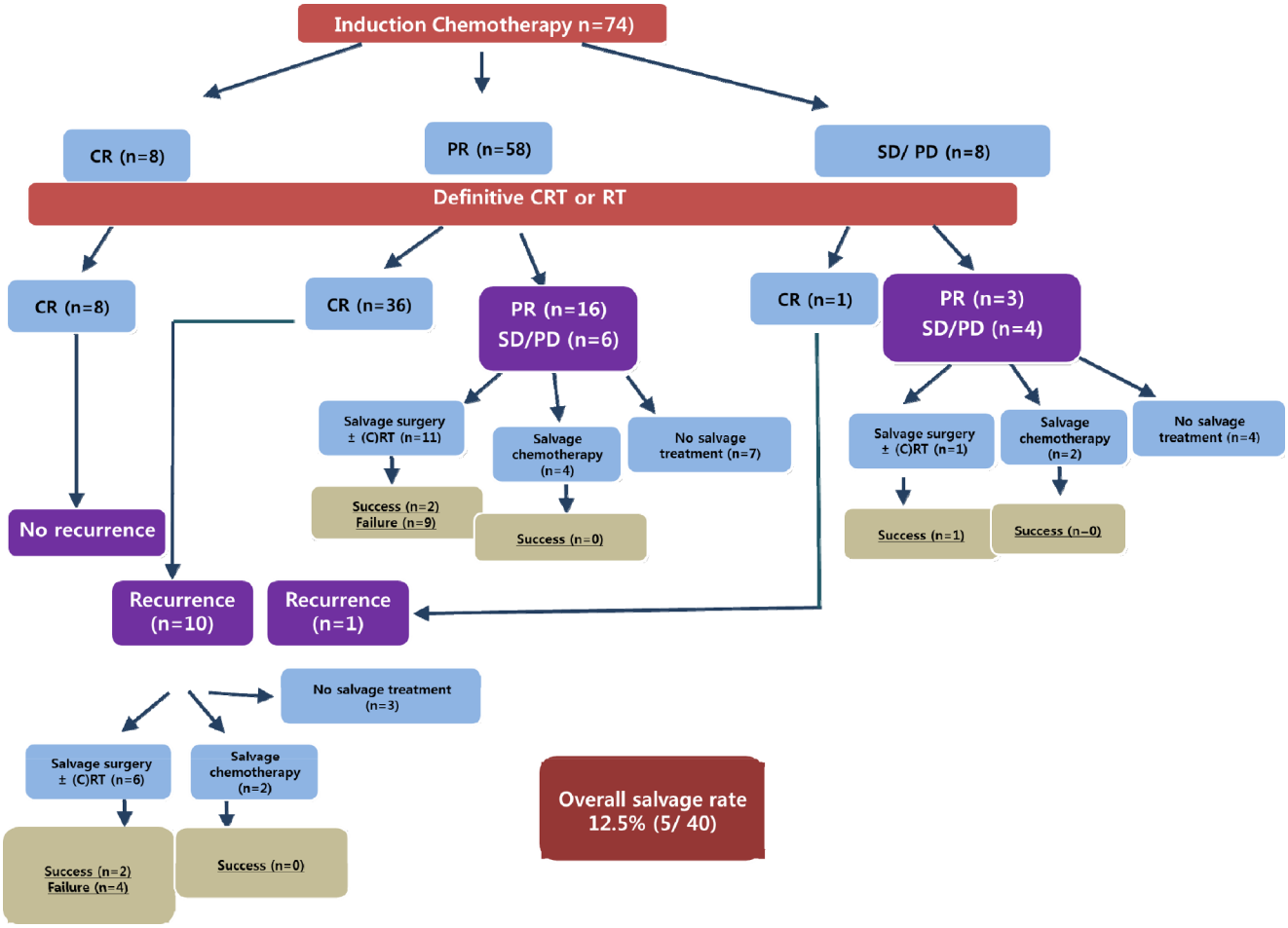


Fig. 2. Treatment outcome of each treatment group. (A) The tumor response for the induction chemotherapy was 8 CR, 58 PR, 4 SD and 4 PD. Induction chemotherapy was followed by definitive CRT or RT in all patients. Of the 58 patients who were considered PR after induction chemotherapy, 36 patients achieved CR after definitive CRT or RT. Of the 8 patients who was considered SD or PD after induction chemotherapy, 1 patient achieved CR after definitive CRT or RT. The finial salvage rate for the residual disease in the ICT group was 10.3%. Recurrent disease developed in 11 patients during the follow-up period. The salvage rate for recurrent disease was 25%. Overall treatment failure defined as residual and recurrent disease occurred in 40 patients and the overall salvage rate was 12.5% for ICT group. Of the 41 patients who had treatment failure in the ICT group, salvage treatment was attempted in 27 patients (57.1%). Nineteen (70.4%) of the 27 patients who attempted salvage treatment were treated with surgery with or without postoperative radiation therapy. Five out of 19 patients were cured after salvage surgery, and the salvage rate was 12.2% with mean follow-up of 16.9 months. (B) Eighteen of 32 patients (56.3%) who had treatment failure in the CRT group underwent salvage treatment. Salvage surgery with or without postoperative radiation therapy was performed in 11 (61.1%) out of 18 patients. Five out of 11 patients were cured after salvage surgery, and the salvage rate (5 of 32 patients) was 15.6% for CRT group with mean follow-up of 11.4 months. (C) Of the 52 patients who had treatment failure in the SRT group, 9 patients (17.3%) attempted salvage treatment. Salvage surgery was performed in 4 (44.4%) out of 9 patients. The salvage rate (2 of 52 patients) was 3.8% for the SRT group with mean follow-up of 8 months. Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; CRT = chemoradiotherapy; RT = radiotherapy; ICT = induction chemotherapy followed by (chemo)radiotherapy.

Surgery-based therapy group

All surgical procedures were performed by a single surgeon (R-YS) in the SRT group to eliminate surgeon bias. The surgical management of the hypopharyngeal SCC depended on the extent of the lesion and the subsites involved. Seventy-four patients (53%) underwent laryngeal preservation surgery in the SRT group (Table S1).

For patients with pyriform apex invasion, with lesions extending to the postcricoid area, or with a high risk of postoperative aspiration, total laryngectomy was required. Total laryngopharyngectomy was performed in twenty-four patients, 30 patients were treated with total laryngectomy and partial pharyngectomy, and 11 were treated with near-total laryngectomy and partial pharyngectomy. Laryngeal preserving surgeries could be performed for a selected group of patients and were performed via a lateral pharyngotomy with or without a transhyoid approach for intraoperative assessment of the extent of the tumor. The type of laryngeal preservation surgery performed depended on the extent of the tumor.

For reconstruction of the surgical defect, primary closure was achieved in 28 cases. In case of larger defects, reconstruction with a free flap (radial forearm free flap in 70, lateral thigh free flap in 17, and jejunal free flap in 4 patients), pectoralis myocutaneous (PMMC) flap (n = 10), gastric pull-up (n = 11) or local flap (n = 4 patients) were performed.

Thirty patients (21.6%) were treated with surgery alone. Surgical treatment was followed by postoperative radiotherapy in 61 patients (for stage higher than pT3/N2, close margin (< 5 mm); 43.9%), and chemoradiation in 48 patients (for positive margin, vascular embolism, perineural invasion or extracapsular nodal spread; 34.5%). The treatment protocol of adjuvant treatment consisted of standard-fractionation radiotherapy (mean dose 59.8 Gy, once-daily fractions) with or without cisplatin 100 mg/m^2 for two or three cycles. All patients underwent at least one-sided elective or therapeutic neck dissection.

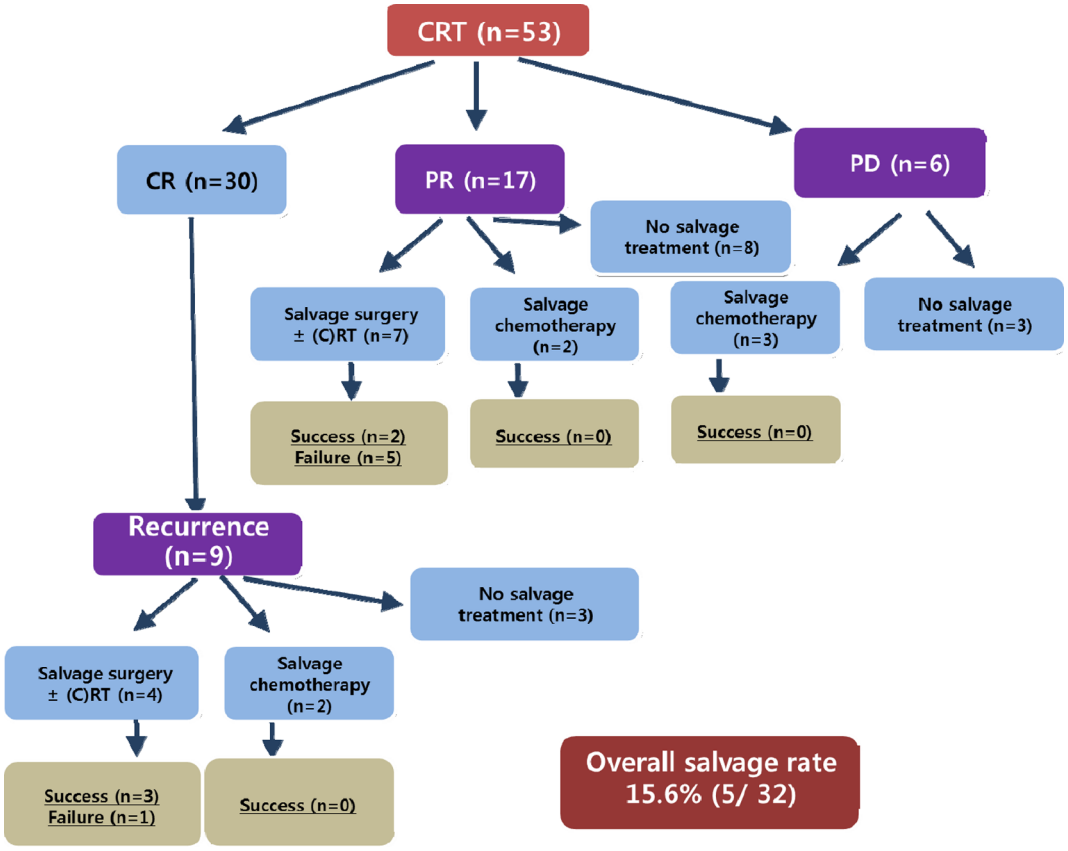


Fig. 2. (*continued*)

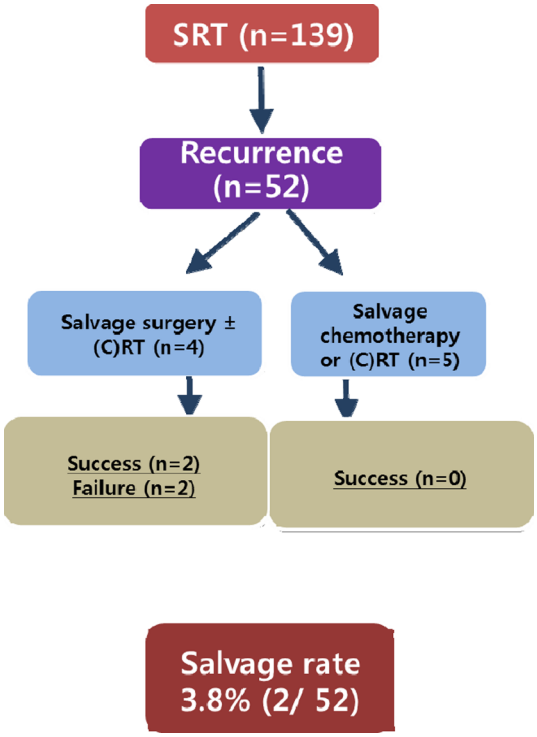
Non-Surgery-based therapy group

The treatment modality of either ICT followed by (chemo)radiotherapy or CRT was decided on according to a multi-disciplinary team approach taking into consideration multiple factors, including size and site of the tumor, possibility of curative resection, general performance status of the patient, and the preference of each patient. ICT regimens were (1) PF: 5-fluorouracil (FU) 1200 mg/m^2 on days 1–4 with cisplatin 60 mg/m^2 on day 1; (2) TPF: docetaxel 70 mg/m^2 on day 1 with 5-FU 1200 mg/m^2 on days 1–3 and cisplatin 40 mg/m^2 on days 2–3; (3); and TP: docetaxel 75 mg/m^2 on day 1 and cisplatin 75 mg/m^2 on day 1. Patients were treated with 2 or 3 cycles of these regimens. Follow-up imaging was performed after 2 or 3 cycles of induction chemotherapy, and the responses were evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1 [4]. CRT (n = 54) or RT (n = 20) was followed, depending on the response and the patient's choice.

Definitive CRT was given with cisplatin 100 mg/m^2 administered every 3 weeks or 35 mg/m^2 every week. All patients received CT-based RT planning with either three-dimensional conformal RT or intensity-modulated radiotherapy (IMRT). Both sides of the neck were included in the RT field and the median RT dose was 70 Gy (range 59.4–72 Gy) for the CRT group. Grossly involved lymph nodes were treated with 66–70 Gy, involved cervical nodal stations were treated with 60–63 Gy and uninvolved nodal stations were treated with 50–54 Gy.

The tumor response was evaluated using RECIST 1.1 criteria [5]. Treatment related toxicities were analyzed according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 3.0. CTCAE.

We officially received the final survival status of patients from the Ministry of the Interior and Safety, Korean Government.



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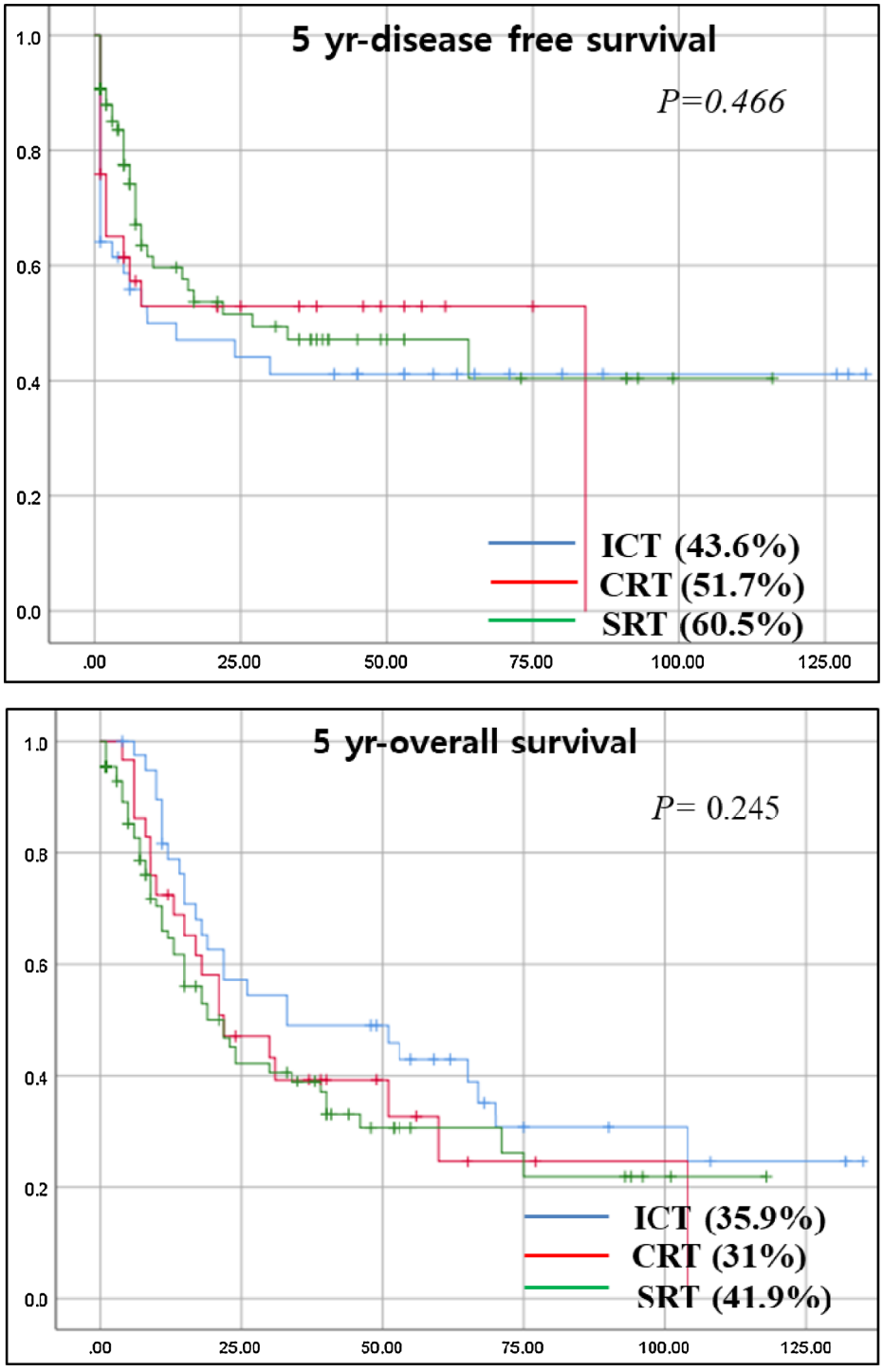
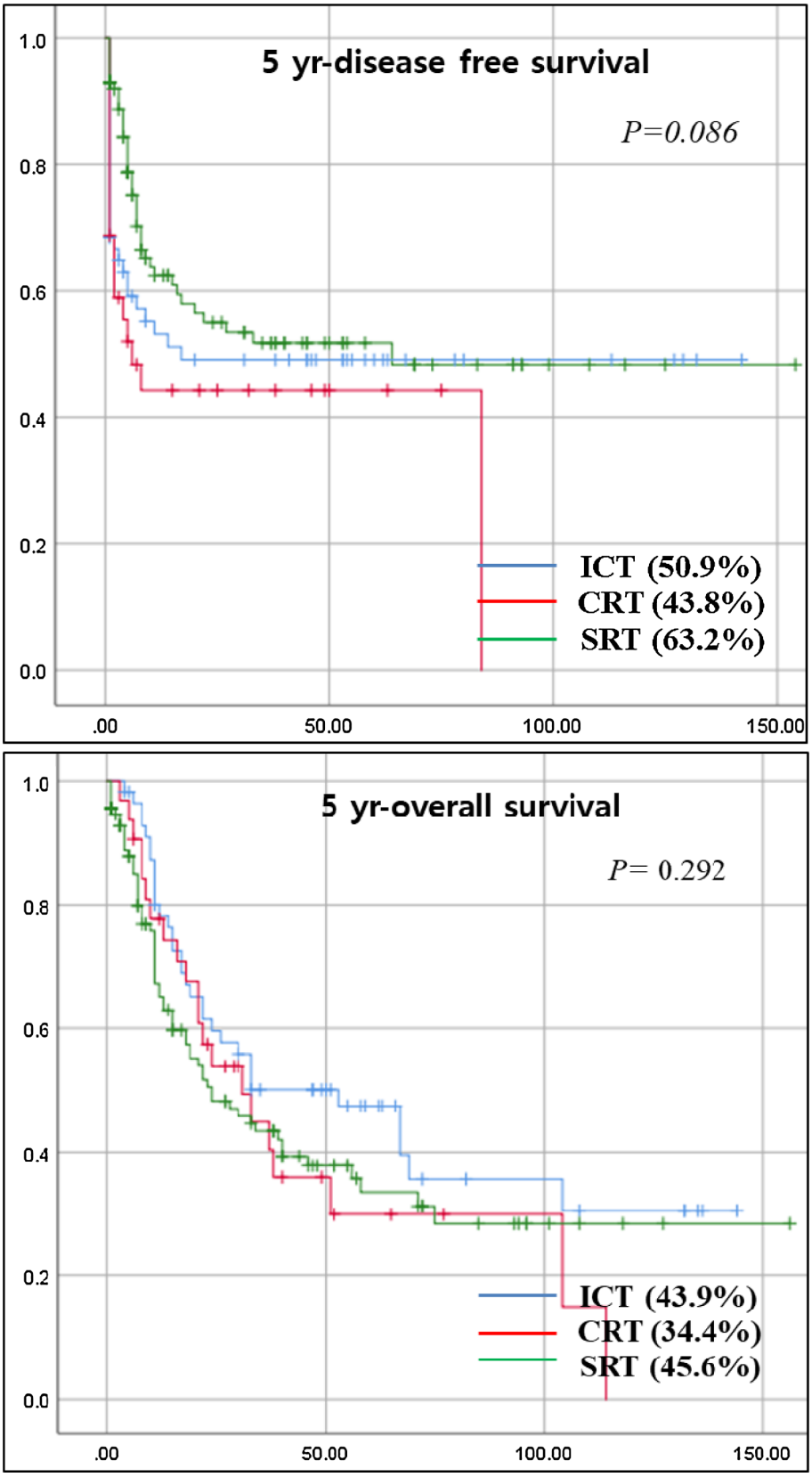


Fig. 3. Oncologic outcome comparison by subgroup (A) DFS after salvage treatment according to initial T3-4 stage subgroup (B) OS after salvage treatment according to initial T3-4 stage subgroup (C) DFS after salvage treatment according to initial N2-3 stage subgroup (D) OS after salvage treatment according to initial N2-3 stage subgroup (E) DFS after salvage treatment according to posterior pharyngeal wall/postcricoid origin tumor subgroup (F) OS after salvage treatment according to posterior pharyngeal wall/postcricoid origin tumor subgroup. *Abbreviations:* DFS = disease-free survival; ICT = induction chemotherapy followed by (chemo) radiotherapy; CRT = chemoradiotherapy; SRT = surgery-based therapy.

Statistical analysis

Relationships between categorical variables were analyzed by Fisher's exact test or the Chi-square test. Comparisons between continuous variables were performed by the one-way ANOVA test. The statistical analyses of patient survival and disease-free interval were based on a comparison of Kaplan–Meier curves by the log-rank test. Cox proportional hazard regression models were used for the multivariate analysis of survival. The chi-square test was used for the additional analysis of categorical variables. A *p*-value less than 0.05 was considered significant. SPSS software version 23 (IBM Co., Armonk, NY, USA) was used for all analyses.



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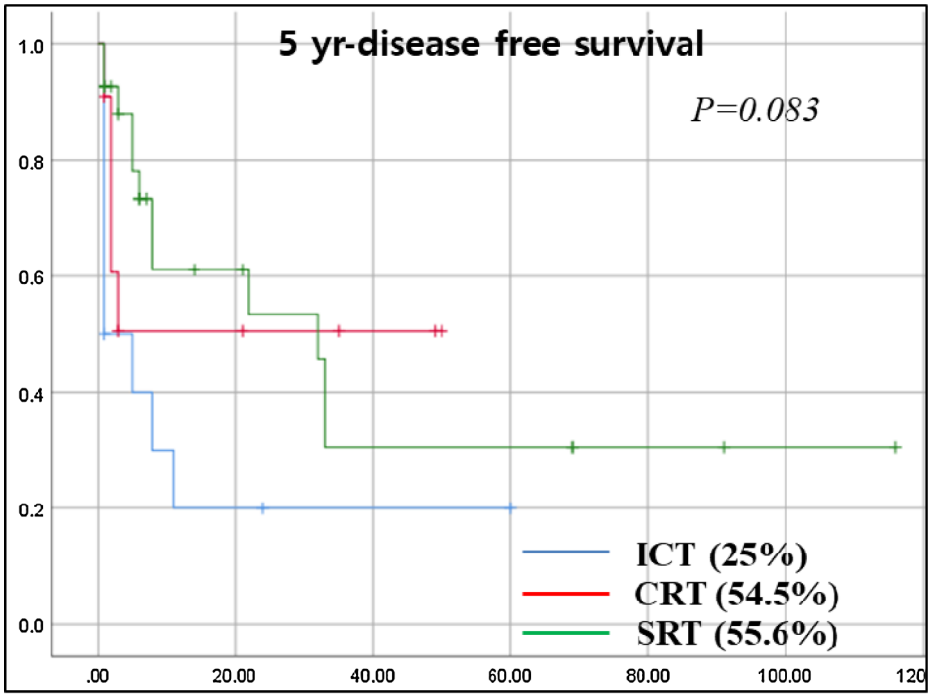

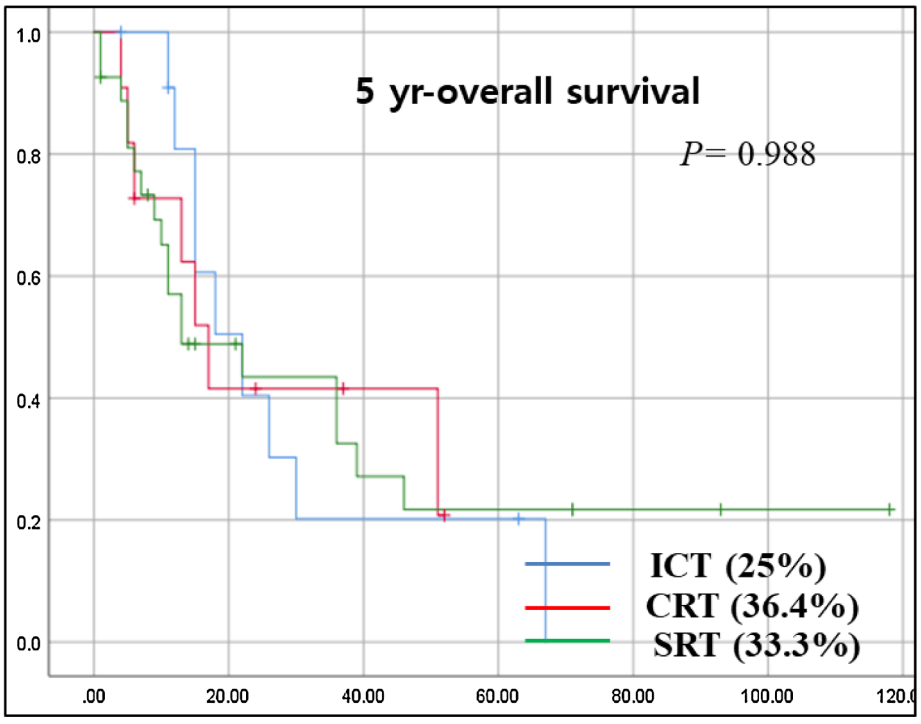

Fig. 3. (*continued*)

Results

Patient demographics

The study group was composed of 249 men and 17 women (mean age 63.7 years, range 41–86 years). The follow-up period ranged from 6 to 156 months (mean 32.9 months). The tumors were classified as T1 in 25 (9.4%) patients, T2 in 87 (32.7%) patients, T3 in 68 (25.6%) patients and T4a in 86 (32.3%) patients. The nodal stages were N0 in 24 (9%), N1 in 39 (14.7%), N2a in 8 (3%), N2b in 134 (50.4%), N2c in 50 (18.8%) and N3 in 11 (4.1%). The original primary site of the tumor was the pyriform sinus in 216 (81.2%) patients, the posterior pharyngeal wall (PPW) in 38 (14.3%) and the post cricoid (PC) in 12 (4.5%).

Clinical features, including age (p = 0.091), original primary site of the tumor (p = 0.328), T stage (p = 0.337) and N stage (p = 0.099) were balanced between the three treatment groups. Sixty-six patients (24.8%) had second primary malignancies, including esophageal cancer, lung cancer, stomach cancer, hepatocellular cancer, cholangiocarcinoma, oral cavity cancer and maxilla cancer. The rate of second primary malignancies was not significantly different among the ICT, CRT and SRT groups (p = 0.063).

Table 2
Dysphagia grade in accordance to CTCAE ver. 3.0 after combined treatment. Grade 3–4 in dysphagia grade was considered percutaneous endoscopic gastrostomy (PEG) dependency. *Abbreviations:* ICT = induction chemotherapy followed by (chemo)radiotherapy; CRT = chemoradiotherapy, SRT = surgery-based therapy.

Dysphagia grade	Adverse events	No (%)		
		ICT (n = 62) Excluding salvage total laryngectomy (n = 12)	CRT (n = 46) Excluding salvage total laryngectomy (n = 7)	SRT (n = 74) Excluding primary total laryngectomy (n = 65)
1	Symptomatic, able to eat regular diet	34 (54.8%)	24 (52.2%)	48 (64.8%)
2	Symptomatic and altered eating/swallowing	20 (32.3%)	14 (30.4%)	19 (25.7%)
3	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	8 (12.9%)	8 (17.4%)	7 (9.5%)
4	Life-threatening consequences; urgent intervention indicated			
5	Death	0 (0%)	0 (0%)	0 (0%)

Overall oncologic outcomes

The 5-year disease-free survival (DFS) and overall survival (OS) of all enrolled patients (n = 266) were 59.4% and 44%, respectively. The effects of various prognostic factors on survival were analyzed. Univariate analysis for DFS and OS revealed advanced T stage (higher than T3, $p = 0.035$ and $p = 0.017$) and posterior pharyngeal wall or postcricoid tumor ($p = 0.025$ and $p = 0.009$) as poor prognostic factors (Table 1). Multivariate analysis revealed that advanced T stage ($p = 0.05$, odds ratio 1.466 and $p = 0.029$, odds ratio 1.454) and posterior pharyngeal wall or postcricoid tumor ($p = 0.047$, odds ratio 1.569 and $p = 0.017$, odds ratio 1.599) were independent factors associated with poor DFS and OS (Table S2).

Outcome comparison by treatment groups

Of the 74 patients in ICT group, complete response (CR) was seen in 8 (10.8%) patients after induction chemotherapy. A partial response (PR) was seen in 58 (78.4%), stable disease (SD) in 4 (5.4%) and progressive disease (PD) in 4 (5.4%) patients. Induction chemotherapy was followed by definitive CRT (n = 54) or RT (n = 20) in all patients. All patients who achieved CR after induction chemothrapy (n = 8) were followed-up without evidence of recurrent disease. Of the 58 patients who was considered PR after induction chemotherapy, 36 (62.1%) patients achieved CR after definitive CRT or RT. Residual disease was identified in 22 (37.9%) patients and the salvage surgery (n = 11) or chemotherapy (n = 4) were attempted. The remaining 7 patients who had residual tumor were not considered for salvage treatment. Two out of 11 patients who underwent salvage surgery for residual tumor were cured and none of the remaining 4 patients who received chemotherapy for their recurrences were salvaged. Of the 8 patients who was considered SD or PD after induction chemotherapy, 1 patient achieved CR after definitive CRT or RT. Residual disease was identified in the other 7 patients and the salvage surgery (n = 1) or chemotherapy (n = 2) were attempted. The patient who underwent salvage surgery was cured after treatment but none of the patients who received chemotherapy were salvaged. The finial salvage rate for the residual disease in the ICT group was 10.3% (3 out of 29 patients). Recurrent disease developed in 11 patients in ICT group with mean follow-up period of 16.4 months. Six patients underwent a salvage surgery and 2 patients were attempted a chemotherapy as a salvage treatment. Two out of 6 patients who underwent surgical treatment for recurrence were salvaged and none of the patients who received chemotherapy for their recurrences were salvaged. The salvage rate for recurrent disease was 25% for the ICT group (2 of 8 patients) with mean follow-up of 19.3 months (Fig. 2). Overall treatment failure defined as residual and recurrent disease occurred in 40 patients in the ICT group (12 local recurrences, 8 regional recurrences, 13 locoregional recurrences, and 7 distant metastasis). Eighteen patients underwent salvage surgery with or without postoperative adjuvant therapy (5 total laryngectomy and partial pharyngectomy, 5 total laryngopharyngoesophagectomy, 2 total laryngopharyngectomy, 1 partial pharyngectomy, and 5 salvage neck dissection only) and 5 out of 18 patients were salvaged after surgery. The overall salvage rate was 12.5% for the ICT group (5 of 40 patients).

A CR was achieved in 56.6% (n = 30) after definitive chemoradiotherapy. A PR was achieved in 32.1% (n = 17) and PD in 11.3% (n = 6) in CRT group. Of the 17 patients who was considered PR after definitive chemoradiotherapy, the salvage surgery (n = 7) or chemotherapy (n = 2) were attempted for treatment of residual disease. The remaining 8 patients who had residual tumor were not considered for salvage treatment. Two out of 7 patients who underwent salvage surgery were cured and none of the patients who received chemotherapy for their recurrences were salvaged. Of the 6 patients who were considered PD after definitive chemotherapy, salvage surgery was not available option and chemotherapy was attempted in 3 patients. None of the patients who received chemotherapy were salvaged. The finial salvage rate for the residual disease in the CRT group was 8.7% (2 out of 23 patients). Recurrent disease developed in 9 patients in CRT group with mean follow-up period of 30.1 months. Four patients underwent a salvage surgery and 2 patients were attempted a chemotherapy as a salvage treatment. Three out of 4 patients who underwent surgical treatment for recurrence were salvaged and none of the patients who received chemotherapy for their recurrences were salvaged. The salvage rate for recurrent disease was 33.3% for the CRT group (3 of 9 patients) with mean follow-up of 21.1 months (Fig. 2). Eighteen of 32 patients (56.3%) who had overall treatment failure in the CRT group (12 local recurrences, 3 regional recurrences, 12 locoregional recurrences, and 5 distant metastasis) underwent salvage treatment. Salvage surgery with or without postoperative adjuvant therapy was performed in 11 (61.1%) out of 18 patients who underwent salvage treatment. Among these 11 patients, four patients underwent a total laryngectomy and partial pharyngectomy, 2 patients had a total laryngopharyngoesophagectomy, 2 had a partial pharyngectomy, 1 had a total laryngopharyngectomy, 1 had a metastasectomy of a single metastatic lung lesion and 1 had a salvage neck dissection only. Five out of 11 patients were cured after salvage surgery, and the overall salvage rate was 15.6% (5 of 32 patients) for the CRT group with mean follow-up of 11.4 months. The other 7 (21.9%) patients underwent chemotherapy but none of these patients were salvaged (Fig. 2).

Of the 139 patients in SRT group, recurrent disease developed in 52 patients (6 local recurrences, 10 regional recurrences, 1 locoregional recurrence, and 35 distant metastasis), and nine patients (17.3%) attempted salvage treatment. Salvage surgery was performed in 4 (44.4%) out of 9 patients who underwent salvage treatment and most of these patients had isolated neck nodal recurrences. Three of these patients (75%) underwent salvage neck dissection for isolated regional recurrence and 1 patient underwent laser resection of a primary recurrence. Among the 4 patients who underwent salvage surgery in the SRT group, 2 patients were rescued. No patients who received chemotherapy as a salvage management were rescued. The salvage rate

Table 3
Respiratory toxicity grade in accordance to CTCAE ver. 3.0 after combined treatment. Grade 3–4 in dysphagia grade was considered decannulation failure. Abbreviations: ICT = induction chemotherapy followed by (chemo)radiotherapy; CRT = chemoradiotherapy, SRT = surgery-based therapy.

Tracheal stenosis grade	Adverse events	No (%)		
		ICT (n = 62) Excluding salvage total laryngectomy (n = 12)	CRT (n = 46) Excluding salvage total laryngectomy (n = 7)	SRT (n = 74) Excluding primary total laryngectomy (n = 65)
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	52 (83.9%)	36 (78.3%)	42 (56.8%)
2	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	5 (8.1%)	4 (8.7%)	20 (27%)
3	Stridor; respiratory distress; hospitalization indicated	1 (1.6%)	2 (4.3%)	12 (16.2%)
4	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	4 (6.4%)	4 (8.7%)	
5	Death		0 (0%)	0 (0%)

was 3.8% (2 of 52 patients) for the SRT group with mean follow-up of 8 months (Fig. 2).

Treatment failure before salvage treatment occurred in 40 patients in the ICT group, 32 patients in the CRT group and 52 patients in the SRT group during the follow-up period. The disease-free survival was significantly better in the SRT group (62.6%) than in the ICT (45.9%) and CRT (39.6%) groups before salvage treatment ($p = 0.05$). However, there were no significant differences in DFS and OS according to the treatment modalities after salvage treatment. Five-year overall DFS after salvage treatment was 52.7% for ICT, 52.8% for CRT and 65.5% for SRT ($p = 0.194$). Five-year OS after salvage treatment was 44.6% for ICT, 39.6% for CRT and 45.3% for SRT ($p = 0.106$) (Fig. S1). The 5-year local failure-free survival (LFFS) was significantly better in the SRT group (68.9% for ICT vs. 62.3% for CRT vs. 92.8% for SRT, $p < 0.001$) and the distant metastasis-free survival (DMFS) was significantly worse in the SRT group (91.9% for ICT vs. 92.5% for CRT vs. 74.8% for SRT, $p = 0.001$). The regional failure-free survival (RFFS) was 73% for ICT, 71.7% for CRT, and 84.2% for SRT ($p = 0.119$) (Fig. S2). The 5-year overall DFS and OS in the salvage treatment group (n = 53) were 25% and 21.2%, respectively.

Approximately half of patients in the ICT (44.6%) and CRT (45.2%) groups died of hypopharyngeal cancer. Meanwhile, significantly more patients died of other causes in the SRT group (15%, 21/139) than in the ICT (4%, 3/74) and CRT (1.9%, 1/53) groups (Table S3).

Oncologic outcome comparison in subgroups by various treatment modalities

For subgroup analysis, we selected the T3-4 stage (n = 154), N2-3 stage (n = 203) and posterior pharyngeal wall/postcricoid origin tumor (n = 51) groups. There were no significant differences in DFS (43.6% for ICT vs. 51.7% for CRT vs. 60.5% for SRT, $p = 0.466$) or OS (35.9% for ICT vs. 31% for CRT vs. 41.9% for SRT, $p = 0.245$) according to the various treatment modalities in the T3-4 subgroup. The DFS (50.9% for ICT vs. 43.8% for CRT vs. 63.2% for SRT, $p = 0.086$) and OS (43.9% for ICT vs. 34.4% for CRT vs. 45.6% for SRT, $p = 0.292$) were not significantly different according to the treatment modalities in the N2-3 subgroup. Patients in the posterior pharyngeal wall/postcricoid origin tumor subgroup showed a DFS of 25% for ICT, 54.5% for CRT, and 55.6% for SRT ($p = 0.083$), and OS was 25% for ICT, 36.4% for CRT, and 33.3% for SRT ($p = 0.988$) (Fig. 3).

Toxicity and laryngeal-function preservation rate

Severe toxicity was defined as any or all of the following events: grade 3 or higher toxicity (RTOG/European Organisation for the Research and Treatment of Cancer late toxicity criteria) clearly related to dysfunction of the larynx and/or pharynx (e.g., airway obstruction or dysphagia) or requirement for a feeding tube/gastrostomy. Table 2 shows the status of toxicities at the last follow-up according to the CTCAE ver. 3.0. Grade 3–4 on the dysphagia scale was considered percutaneous endoscopic gastrostomy (PEG)-dependency. Among the 62 patients in the ICT group (excluding salvage total laryngectomy, n = 12), 8 patients had PEG dependency (12.9%). The PEG dependency rate was 17.4% (8 patients out of 46 patients) in the CRT group (excluding salvage total laryngectomy, n = 7) and 9.5% (7 patients out of 74 patients) in the SRT group (excluding primary total laryngectomy, n = 65). The PEG dependency rate was not significantly different among the ICT, CRT and SRT groups ($P = 0.444$). Respiratory toxicities are listed in Table 3, and grade 3–4 in the dysphagia grade was considered decannulation failure. Among the 62 patients in the ICT group (excluding salvage total laryngectomy, n = 12), 5 patients failed decannulation (8.1%). The decannulation failure rate was 13% (6 patients out of 46 patients) in the CRT group (excluding salvage total laryngectomy, n = 7) and 16.2% (12 patients out of 74 patients) in the SRT group (excluding primary total laryngectomy, n = 65). The decannulation failure rate was not significantly different among the ICT,

Table 4
The comparison of final laryngeal preservation rate between different treatment modalities. Value indicated by '*' is statistically significant. *Abbreviations:* ICT = induction chemotherapy followed by (chemo)radiotherapy; CRT = chemoradiotherapy, SRT = surgery-based therapy.

	ICT (n = 74)	CRT (n = 53)	SRT (n = 139)	*p* value
Total laryngectomy	12 (16.2%)	7 (13.2%)	65 (46.8%)	
PEG dependency	4 (5.4%)	2 (3.8%)	0 (0%)	
Decannulation failure	1 (1.4%)	0 (0%)	5 (3.6%)	
PEG dependency & decannulation failure	4 (5.4%)	6 (11.3%)	7 (5.0%)	
Laryngeal preservation	53 (71.6%)	38 (71.7%)	62 (44.6%)	$p < 0.001$*

CRT and SRT groups ($P = 0.361$). The final laryngeal preservation rate was significantly lower in the SRT group (44.6%) than in the ICT (71.6%) and CRT groups (71.7%) (Table 4).

The postoperative complications in the primary and salvage surgery group are listed in Table S4. Eleven (7.9%) and 8 patients (24.2%) developed postoperative pharyngocutaneous fistula and wound infections in the primary and salvage surgery groups, respectively ($p = 0.007$). The flap failure rate was significantly higher in the salvage surgery group (1.4% vs. 12.1%, $p = 0.003$). One (0.7%) and 3 patients (9.1%) developed carotid blowout in the primary and salvage surgery groups, respectively ($p = 0.023$).

Discussion

Hypopharyngeal SCC is a highly aggressive cancer that is notorious for poor prognosis. Moreover, these tumors and their treatment affect a patient's ability to communicate, swallow and function in society. When managing patients with these diseases, the physician should be mindful of the importance of maintaining quality of life, in addition to the importance of a definitive cure. Long-term survival, a primary goal, should be balanced with the known sequelae of therapy [6].

Definitive RT alone or partial laryngopharyngectomy are treatment options for early-stage hypopharyngeal SCC [2,3]. However, there is no clear advantage of one treatment option over another for resectable locally advanced hypopharyngeal cancer (stage III/IV). For decades, the standard treatment option that provided the best oncologic outcomes was the combination of pharyngectomy with reconstruction and total laryngectomy, followed by (chemo)radiotherapy. However, definitive chemoradiotherapy has gained increasing popularity as the definitive treatment in laryngeal cancer in the context of the global trend toward organ-preserving therapy. Unfortunately, the safety and efficacy of organ preservation treatment in locally advanced hypopharyngeal SCC have not been thoroughly evaluated, unlike in carcinoma of the larynx, precluding a definitive conclusion regarding the best treatment option [7].

Organ preservation treatment protocols require the patient's understanding that surgical salvage is a part of the treatment. In addition, it is incumbent on the treating physician to closely follow the patient's tumor because prompt surgical salvage can ensure survival similar to that of conventional treatment. The European Organization for Research and Treatment of Cancer (EORTC) performed randomized trials on hypopharyngeal cancer specifically comparing the results of initial surgery-based versus non-surgery-based treatment [8]. There was no statistically significant difference between the surgery-based and non-surgery-based treatment groups with respect to 5-year locoregional and overall DFS rates. They reported the final laryngeal preservation rate as 35%. Meanwhile, Beauvillain et al. [9] compared the treatment result of 92 patients with resectable hypopharyngeal cancer and they reported that the 5-year DFS and LFFS were significantly better in the surgery arm than in the radiotherapy arm.

As far as we know, the present study is the first in the literature to make comparisons among ICT, CRT and SRT groups, all feasible options for locally advanced resectable hypopharyngeal cancer. In the present study, the overall 5-year DFS and OS were 59.4% and 44%, respectively, higher than or at least comparable to the results of previous reports [8,10]. The final DFS and OS after salvage treatment for all three treatment modalities groups were not significantly different in our study. The 5-year overall DFS after salvage treatment were 52.7% for ICT, 52.8% for CRT and 65.5% for SRT ($p = 0.194$), and the 5-year OS after salvage treatment were 44.6% for ICT, 39.6% for CRT and 45.3% for SRT group ($p = 0.106$).

Induction chemotherapy demonstrated a 5% survival rate increase for trials specifically using a cisplatin/5-FU combination [11] and a reduction in the incidence of distant metastases [12]. However, induction chemotherapy showed minimal survival advantage in our study. Although open conservation laryngeal surgery for hypopharyngeal cancer is rarely considered suitable for advanced tumors for oncological and functional reasons, seventy-four out of 139 (53%) patients in our study underwent open laryngeal preservation surgery in the SRT group. Joo et al. [13] reported 5-year OS and DFS as 63% and 67%, respectively, and the laryngeal preservation rate was 88%. Plouin-Gaudon et al. [14] reported 5-year OS and DFS as 50% and 65%, respectively, and the laryngeal preservation was 80% in selected pyriform sinus cancer patients. We analyzed only one surgeon's data in the SRT group to minimize the bias of oncological and functional outcomes in this multicenter study including 74 patients who underwent laryngeal preservation surgery.

Surgery followed by (chemo)radiation is consistently preferred for patients with T3-4 stage hypopharyngeal SCC. [15] However, there was no significant difference in DFS and OS according to the various treatment modalities in the T3-4 subgroup. There were also no differences in DFS and OS according to the treatment modalities in the N2-3 subgroup in our result.

Salvage surgery for locoregional failure was more effective in the ICT and CRT groups than in the SRT group. In the ICT group, 18 out of 40 recurrent patients (45%) had attempted salvage surgery, and the salvage efforts were successful in 5 of these patients. Eleven of 32 patients (34.4%) who had treatment failure in the CRT group underwent salvage surgery and five of 11 patients were cured after salvage surgery. Outcome of salvage treatment in the SRT group was more unfavorable. Four of the 52 recurrent patients (7.7%) attempted salvage through surgical treatment. The surgical salvage rate (2 of 52 patients) was 3.8% for the SRT group. Most head and neck oncologists agree that a salvage surgical procedure provides the best chance of long-term disease control and possible cure for operable patients with resectable, recurrent cancers [16]. However, the overall postoperative complication rate in salvage surgery is quite high [17]. In our study, all major postoperative complications were significantly greater in the salvage surgery group.

There are concerns for increased toxicity after treatment of hypopharyngeal cancer, including dysphagia and airway toxicity because of the anatomic and physiologic perspectives. In our study, the PEG-dependency rate was 12.9% in the ICT group, 17.4% in the CRT group, and 9.5% in the SRT group and was not significantly different among the ICT, CRT and SRT groups ($P = 0.444$). The decannulation failure rate was 8.1% in the ICT group, 13% in the CRT group, and 16.2% for the SRT group and was not significantly different among the ICT, CRT and SRT groups ($P = 0.361$). However, the final laryngeal preservation rate for overall patients was significantly lower in the SRT group (44.6%) than in the ICT (71.6%) and CRT groups (71.7%).

In general, in cancer statistics, OS rate is usually more than DFS survival rate. However, the 5-year OS survival is lower than DFS in this study. This discrepancy is supposed to be related to the treatment-related mortality (especially in SRT group with laryngeal preservation surgery) and unknown etiology of death.

In conclusion, ICT and CRT provide treatment outcomes that are comparable to those of SRT for stage III/IV locally advanced hypopharyngeal SCC. However, the relatively low chance of cure and high risk of complications should be taken into account when considering salvage surgery.

Disclosure

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Conflict of interest statement

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2018.12.015.

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