Head and Neck

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Association of Time Interval From Surgery to Postoperative Radiation Therapy With Survival for Patients With Head and Neck Cancer

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두경부암 환자의 수술에서 수술 후 방사선 치료 시작까지의 시간 간격과 생존율의 연관성에 관한 연구

최석열[1] · 조용민[1] · 오경호[2] · 조재구[1] · 백승국[3] · 권순영[2] · 정광윤[3] · 우정수[1]

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Background and Objectives Oncologic effect of initiating postoperative radiotherapy (PORT) in adherance with the National Comprehensive Cancer Network Guidelines remains uncertain. This study aimed to reassess the impact of time of initiating PORT over 6 weeks on survival.

Subjects and Method Patients were dichotomized into groups according to the time of initiation, those that initiated PORT ≤6 weeks and those that initiated PORT >6 weeks postoperatively. The Kaplan–Meier, univariate, and multivariate analyses were then conducted. Outcome measures were overall survival (OS) and progression-free survival (PFS).

Results OS rates at 5 years for the group that initiated PORT ≤6 weeks and those that initiated PORT >6 weeks were 86.3% and 72.9%, respectively (log-rank p=0.26). PFS rates at 5 years for the group of PORT ≤6 and for the group of PORT >6 weeks were 65.6% and 65.9%, respectively (log-rank p=0.95).

Conclusion In this study, there was no statistical difference in OS and PFS rate between groups that began initiation of PORT ≤6 and those that began >6 weeks. In the future, retrospective studies with more patients will be needed to further confirm our observation from this study.

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Keywords Head and neck cancer; National Comprehensive Cancer Network Guidelines; Overall survival; Postoperative radiotherapy; Progression-free survival.

Introduction

The treatment of head and neck cancer requires multimodality therapy, including surgery, radiotherapy, or chemotherapy. Recent advances in each treatment modality have contributed to improved survival rates; however, the oncologic

outcomes remain poor in general. Therefore, many studies have investigated strategies to improve the survival rates.

Timely diagnosis and treatment have been one of the key strategies to improve the overall survival (OS) rates of patients with head and neck cancer.[1,2] According to the National Comprehensive Cancer Network (NCCN) Treatment Guidelines, the recommended interval between curative surgery and beginning of postoperative radiotherapy (PORT) is ≤6 weeks.[3] It is of course recommended to avoid unnecessary delay in initiating PORT, but there may be cases where delays in PORT are inevitable in low to middle-income countries. Wound healing problems, insurance and socioeconomic issues, medical comorbidities, and limited availability in department of radiation oncology can also be other causes of inevitable delays in PORT. Therefore, doubts have been arisen as to whether not strictly adhering to 6-week period affects the oncologic outcomes of treatment despite the recent advancement in managing head and neck cancer. Indeed, NCCN guideline is consistent with that in a systematic review of studies published more than 20 years ago, which found that the rate of local recurrence of head and neck cancers significantly increased in patients whose time taken from surgery to PORT was >6 weeks.[4] However, several studies reporting no oncologic benefit in adhering to the NCCN guidelines have been published recently.[5-8] It has been argued that the recent advances in the treatment, such as multidisciplinary evaluation, modern surgical reconstruction technique, sophisticated radiation planning, and concurrent chemotherapy, have attributed to it.[9,10] Therefore, the oncologic effect of commencing PORT before 6 weeks after surgery remains uncertain, and it is worthwhile to reassess whether delays in initiating PORT are significantly associated with decreased survival rates.

The objective of this study was to evaluate the impact of delayed PORT >6 weeks postoperatively on OS and progression-free survival (PFS) in patients with head and neck cancer. Moreover, we investigated whether the earlier initiation of PORT before 5 weeks after surgery was associated with improved OS and PFS and whether delayed PORT longer than 7 weeks postoperatively was associated with impaired OS and PFS.

Subjects and Methods

This was a retrospective study of 211 patients whose initial treatment for head and neck cancer consisted of curative-intent surgery and PORT at the Korea University Medical Center between 2009 and 2018. None of them had received prior cancer therapy before surgery. Patients who underwent palliative-intent surgery, induction chemotherapy, or preoperative radiation therapy or did not complete the entire course of radiation therapy as prescribed were excluded. Patients with synchronous multiple primary cancers were also excluded from the study. The Institutional Review Board (IRB) of the Korea University Medical Center approved this study (IRB No. 2022GR0310).

Electronic patient records were reviewed to obtain patient (age and sex), tumor (subsite, T and N classification, and pathologic stages), and treatment (surgical margin, radiation duration, radiation dose per fraction, total radiation dose, and concurrent chemotherapy) characteristics. Follow-up was performed from the day of surgery. The patients were staged according to the seventh edition of the American Joint Committee on Cancer Staging of Head and Neck Cancer, and pathologic staging was based on surgical and pathologic findings. The tumor sites included the oral cavity, oropharynx, larynx, hypopharynx, and major salivary glands. Postoperative adjuvant radiotherapy or concurrent chemoradiotherapy were indicated for patients of oral cavity, oropharynx, hypopharynx, and larynx cancer with extranodal extension, positive or close margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular invasion, or lymphatic invasion. For major salivary gland cancer, postoperative adjuvant radiotherapy or concurrent chemoradiotherapy were indicated in case of intermediate or high grade, close or positive margins, neural/perineural invasion, lymph node metastases, lymphatic/vascular invasion, or pT3 or pT4 primary tumors. Time interval between surgery and initiation of postoperative radiotherapy (S-PORT), which was defined as the number of days from the date of the most definitive surgery to the first day of PORT, was also measured. Categorical variables were grouped for analysis.

Outcome measures included OS and PFS. OS was calculated from the date of surgery to death or the last follow-up. PFS was calculated from the date of surgery to locoregional recurrence, distant metastasis, death, or the last follow-up.

Patients were dichotomized into groups of S-PORT ≤6 and >6 weeks postoperatively, and differences in proportions between those subgroups were tested using the χ^2 statistic and Fisher's exact test. The Kaplan−Meier method was used for the univariate survival analysis of patients with S-PORT ≤6 or >6 weeks postoperatively, and the log-rank test was utilized

for the comparison between curves. Univariate and multivariate Cox proportional hazards regression analyses were performed to assess variables related to OS and PFS and their hazard ratios. Variables with a p value of <0.10 in the univariate analysis were selected for the multivariate Cox proportional hazards regression analysis. For categorical variables with unknown or missing information, an unknown category was included but omitted from the univariate and multivariate Cox proportional hazards regression analyses.

In addition, S-PORT was analyzed as a categorical variable to determine whether the early or late initiation of PORT affects survival. Patients were grouped according to S-PORT: ≤5, 5–7, and >7 weeks (the intervals were not inclusive of the lower bound and were inclusive of the upper bound). For intuitive clinical interpretation, S-PORT was analyzed as a categorical variable instead of a continuous variable. Statistical analysis was conducted using Statistical Package for the Social Sciences software (SPSS 26.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at a p value of <0.05.

Results

A total of 211 patients with head and neck cancer who underwent surgery and PORT were included in the study, and the median follow-up period was approximately 4.7 years. Patient (age and sex), tumor (subsite, T and N classification, and pathologic stages), and treatment (surgical margin, radiation duration, radiation dose per fraction, total radiation dose, and concurrent chemotherapy) characteristics are summarized in Table 1. The mean age at diagnosis was 61.6 (range, 22–93) years, and the majority of the tumors were stage IV. Overall, 14.7% of the patients initiated PORT over 6 weeks after surgery, and detailed distribution of patients according to S-PORT is shown in Fig. 1. S-PORT ranged from 12 to 167 days, and the mean was 36 days. There were multiple reasons for delays, including delayed wound healing, medical complications, and social issues. There was no significant difference in the characteristics between the groups of S-PORT ≤6 and >6 weeks except pathologic stage. The proportion of stage III in the group of S-PORT ≤6 weeks was relatively greater than that in the group of >6 weeks, but the proportion of stage II and IV showed the opposite results. The higher the stage, the more postoperative complications may occur after surgery, but the causes of delay in PORT initiation were not completely identified due to the retrospective nature of this study.

The OS rates at 5 years for the groups of S-PORT ≤6 and

Table 1. Patient, tumor, and treatment characteristics

Variable	Total patients (n=211)	S-PORT ≤6 weeks (n=180)	S-PORT >6 weeks (n=31)	p value
Age				0.54
<50 yr	35 (16.6)	31 (17.2)	4 (12.9)	
50–59 yr	56 (26.5)	49 (27.2)	7 (22.6)	
60–69 yr	67 (31.7)	58 (32.2)	9 (29.0)	
≥70 yr	53 (25.2)	42 (23.4)	11 (35.5)	
Sex				0.42
Male	173 (82.0)	146 (81.1)	27 (87.1)	
Female	38 (18.0)	34 (18.9)	4 (12.9)	
Primary site				0.45
Oral cavity	42 (19.9)	36 (20.0)	6 (19.3)	
Oropharynx	59 (28.0)	52 (28.9)	7 (22.6)	
Larynx	47 (22.3)	42 (23.3)	5 (16.2)	
Hypopharynx	23 (10.9)	17 (9.4)	6 (19.3)	
Salivary gland	40 (18.9)	33 (18.4)	7 (22.6)	
T classification				0.08
1	46 (21.8)	42 (23.3)	4 (12.9)	
2	73 (34.6)	61 (33.9)	12 (38.7)	
3	42 (20.0)	39 (21.6)	3 (9.7)	
4	50 (23.6)	38 (21.2)	12 (38.7)	
N classification				0.50
0	81 (38.5)	67 (37.2)	14 (45.1)	
1	19 (9.0)	18 (10.0)	1 (3.2)	
2	102 (48.3)	88 (48.9)	14 (45.1)	
3	9 (4.2)	7 (3.9)	2 (6.6)	
Pathologic stage				0.04
I	17 (8.0)	16 (8.9)	1 (3.2)	
II	26 (12.3)	19 (10.5)	7 (22.6)	
III	35 (16.6)	34 (18.9)	1 (3.2)	
IV	133 (63.1)	111 (61.7)	22 (71.0)	
Surgical margin				0.26
Negative	122 (57.8)	100 (55.5)	22 (71.0)	
Positive	82 (38.8)	74 (41.1)	8 (25.8)	
Unknown	7 (3.4)	6 (3.4)	1 (3.2)	
Chemotherapy				0.40
No	101 (47.8)	84 (46.7)	17 (54.8)	
Yes	110 (52.2)	96 (53.3)	14 (45.2)	
PORT duration				0.52
≤39 day	16 (7.6)	12 (6.7)	4 (12.9)	
40–49 day	91 (43.1)	79 (43.9)	12 (38.7)	
50–59 day	93 (44.1)	81 (45.0)	12 (38.7)	
≥60 day	11 (5.2)	8 (4.4)	3 (9.7)	
PORT dose per fraction				0.85
180 cGy	105 (49.7)	91 (50.5)	14 (45.1)	
200 cGy	48 (22.7)	40 (22.2)	8 (25.8)	
220 cGy	58 (27.6)	49 (27.3)	9 (29.1)	

Table 1. Patient, tumor, and treatment characteristics (continued)

Variable	Total patients (n=211)	S-PORT ≤6 weeks (n=180)	S-PORT >6 weeks (n=31)	*p* value
PORT dose				0.32
≤44.9 Gy	5 (2.4)	3 (1.7)	2 (6.5)	
45–54.9 Gy	6 (2.8)	4 (2.2)	2 (6.5)	
55–64.9 Gy	98 (46.4)	85 (47.2)	13 (41.9)	
≥65 Gy	102 (48.3)	88 (48.9)	14 (45.1)	

Data are presented as n (%). S-PORT, time interval between surgery and initiation of postoperative radiotherapy; PORT, postoperative radiotherapy

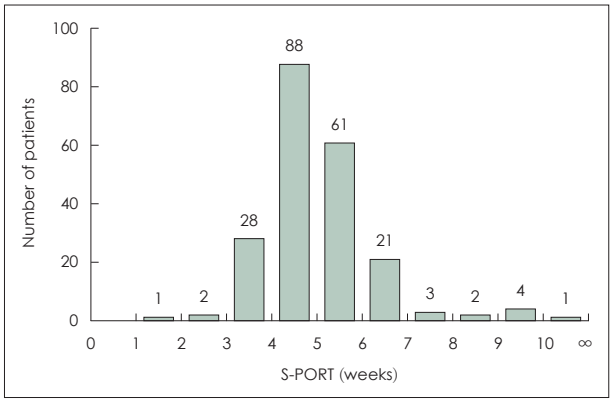
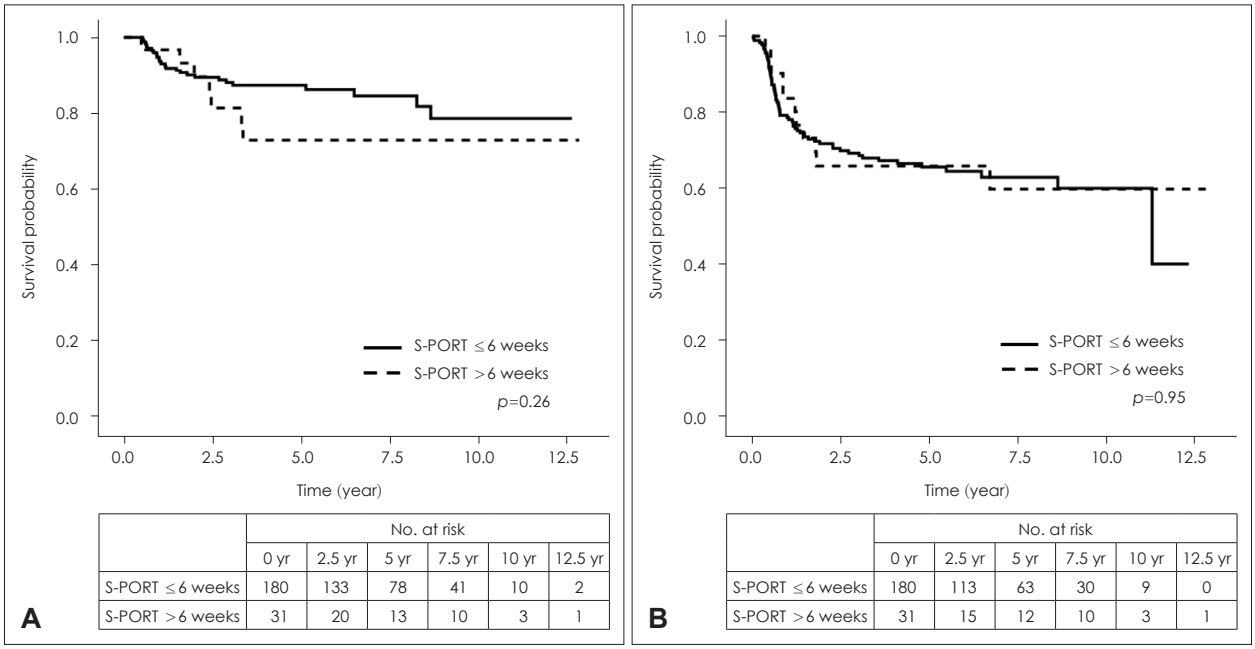


Fig. 1. Distribution of patients according to S-PORT. S-PORT, time interval between surgery and the initiation of postoperative radiotherapy.

>6 weeks were 86.3% and 72.9%, respectively. The PFS at 5 years for the groups of S-PORT ≤6 and >6 weeks were 65.6% and 65.9%, respectively. However, there was no statistical difference between the groups of S-PORT ≤6 and >6 weeks in either OS or PFS (log-rank p>0.05) (Fig. 2).

Univariate and multivariate analyses were conducted to determine whether delays were significantly associated with decreased OS or PFS (Tables 2 and 3). In univariate analysis, N2 classification was significantly associated with OS. Multivariate analysis demonstrated that the age of >60 years, oropharynx cancer, and N2 classification were significantly associated with OS. For PFS, univariate analysis demonstrated a significant association with the age of >70 years, oropharynx cancer, T classification higher than T1, N2 and N3 classification, positive surgical margin, and concurrent chemotherapy. Multivariate analysis demonstrated that the age of >70 years, oropharynx and laryngeal cancer, T classification higher than T1, and N3 classification were significantly associated with PFS.

An additional analysis stratifying S-PORT into ≤5, 5–7, and >7 weeks and their association with OS or PFS was performed. As a result, 56.4% (n=119), 38.8% (n=82), and 4.8% (n=10) of the patients started PORT ≤5, 5–7, and >7 weeks after surgery, respectively. The Kaplan–Meier estimates of OS and PFS for the groups of S-PORT ≤5, 5–7, and >7 weeks were calculated. In overall, there was no statistical difference among those groups in either OS or PFS (log-rank p>0.05) (Fig. 3). When



	No. at risk					
	0 yr	2.5 yr	5 yr	7.5 yr	10 yr	12.5 yr
S-PORT ≤6 weeks	180	133	78	41	10	2
S-PORT >6 weeks	31	20	13	10	3	1

	No. at risk					
	0 yr	2.5 yr	5 yr	7.5 yr	10 yr	12.5 yr
S-PORT ≤6 weeks	180	113	63	30	9	0
S-PORT >6 weeks	31	15	12	10	3	1

Fig. 2. Kaplan–Meier curves of overall survival (A) and progression-free survival (B) for the groups of S-PORT ≤6 and >6 weeks. S-PORT, time interval between surgery and the initiation of postoperative radiotherapy.

Table 2. Results of the univariate and multivariate analysis for overall survival

Patient variable	Univariate analysis	*p* value	Multivariate analysis	*p* value
S-PORT >6 weeks	1.58 (0.68–3.67)	0.32	–*	
Age				
<50 yr	1 (reference)	0.05	1 (reference)	0.01
50–59 yr	0.96 (0.23–4.05)	0.96	1.21 (0.28–5.14)	0.79
60–69 yr	2.66 (0.76–9.27)	0.12	4.08 (1.15–14.43)	0.03
≥70 yr	2.99 (0.82–10.89)	0.09	4.52 (1.16–17.57)	0.03
Sex				
Male	1 (reference)		–*	
Female	0.78 (0.30–2.04)	0.62		
Primary site				
Oral cavity	1 (reference)	0.36	1 (reference)	0.21
Oropharynx	0.37 (0.13–1.03)	0.06	0.31 (0.10–0.94)	0.04
Larynx	0.72 (0.27–1.88)	0.71	0.49 (0.13–1.79)	0.28
Hypopharynx	0.38 (0.08–1.73)	0.21	0.28 (0.05–1.41)	0.12
Salivary gland	0.69 (0.26–1.82)	0.46	0.72 (0.22–2.35)	0.59
T classification				
1	1 (reference)	0.38	1 (reference)	0.33
2	1.83 (0.59–5.68)	0.29	2.24 (0.64–7.83)	0.20
3	2.78 (0.85–9.06)	0.09	2.39 (0.65–8.70)	0.18
4	1.66 (0.48–5.69)	0.41	1.19 (0.30–4.64)	0.80
N classification				
0	1 (reference)	0.04	1 (reference)	0.01
1	0.50 (0.06–4.11)	0.52	0.42 (0.05–3.53)	0.42
2	2.50 (1.06–5.85)	0.03	3.31 (1.32–8.26)	0.01
3	2.84 (0.58–13.79)	0.19	2.01 (0.39–10.21)	0.40
Pathologic stage				
I	1 (reference)	0.38		
II	19609.29 (0–7.19E+90)	0.92	–*	
III	12004.56 (0–4.04E+90)	0.92		
IV	32152.38 (0–1.17E+91)	0.91		
Surgical margin				
Negative	1 (reference)		–*	
Positive	0.98 (0.48–1.99)	0.97		
Chemotherapy				
No	1 (reference)		–*	
Yes	1.71 (0.82–3.56)	0.14		
PORT duration				
≤39 day	1 (reference)	0.01	1 (reference)	0.00
40–49 day	0.51 (0.10–2.54)	0.41	0.39 (0.07–1.98)	0.25
50–59 day	1.69 (0.39–7.24)	0.48	1.62 (0.37–7.03)	0.52
≥60 day	4.36 (0.79–24.03)	0.09	3.53 (0.61–20.48)	0.16
PORT dose				
≤44.9 Gy	1 (reference)	0.96		
45–54.9 Gy	8194.99 (0–3.88E+92)	0.93	–*	
55–64.9 Gy	7643.94 (0–3.59E+92)	0.93		
≥65 Gy	9178.82 (0–4.31E+92)	0.93		

Data are presented as hazard ratio (95% confidence interval). *dropped out of the final multivariate model. S-PORT, time interval between surgery and initiation of postoperative radiotherapy; PORT, postoperative radiotherapy

Table 3. Results of the univariate and multivariate analysis for progression-free survival

Patient variable	Univariate analysis	*p* value	Multivariate analysis	*p* value
S-PORT >6 weeks	1.00 (0.52–1.90)	0.99	–*	
Age				
<50 yr	1 (reference)	0.17	1 (reference)	0.01
50–59 yr	1.96 (0.83–4.63)	0.12	2.29 (0.95–5.55)	0.06
60–69 yr	1.87 (0.80–4.737)	0.14	1.92 (0.80–4.58)	0.14
≥70 yr	2.61 (1.11–6.16)	0.03	4.42 (1.72–11.37)	0.00
Sex				
Male	1 (reference)		1 (reference)	
Female	0.50 (0.24–1.05)	0.07	0.71 (0.32–1.58)	0.41
Primary site				
Oral cavity	1 (reference)	0.09	1 (reference)	0.00
Oropharynx	0.42 (0.21–0.84)	0.01	0.29 (0.14–0.62)	0.00
Larynx	0.57 (0.28–1.17)	0.13	0.33 (0.13–0.81)	0.02
Hypopharynx	0.95 (0.44–2.05)	0.91	0.78 (0.33–1.85)	0.57
Salivary gland	0.79 (0.41–1.53)	0.49	0.72 (0.35–1.51)	0.39
T classification				
1	1 (reference)	0.00	1 (reference)	0.00
2	3.05 (1.15–8.04)	0.02	3.64 (1.35–9.82)	0.01
3	5.26 (1.97–14.05)	0.00	6.56 (2.35–18.20)	0.00
4	5.61 (2.13–14.73)	0.00	5.09 (1.90–13.61)	0.00
N classification				
0	1 (reference)	0.01	1 (reference)	0.08
1	0.76 (0.26–2.25)	0.62	0.85 (0.28–2.63)	0.79
2	1.75 (1.01–3.01)	0.04	1.71 (0.92–3.16)	0.08
3	4.64 (1.94–11.11)	0.00	2.87 (1.08–7.58)	0.03
Pathologic stage				
I	1 (reference)	0.09		
II	16870.43 (0–2.63E+59)	0.88	–*	
III	14364.77 (0–2.24E+59)	0.88		
IV	32441.19 (0–5.06E+59)	0.87		
Surgical margin				
Negative	1 (reference)		1 (reference)	
Positive	1.62 (1.02–2.58)	0.04	1.43 (0.85–2.41)	0.17
Chemotherapy				
No	1 (reference)		1 (reference)	
Yes	1.75 (1.08–2.83)	0.02	1.82 (0.95–3.48)	0.07
PORT duration				
≤39 day	1 (reference)	0.15	1 (reference)	0.80
40–49 day	1.32 (0.46–3.78)	0.59	1.00 (0.33–3.06)	0.99
50–59 day	1.63 (0.57–4.61)	0.35	1.09 (0.36–3.28)	0.86
≥60 day	3.41 (0.95–12.18)	0.06	1.69 (0.38–7.35)	0.48
PORT dose				
≤44.9 Gy	1 (reference)	0.75		
45–54.9 Gy	1.26 (0.11–14.47)	0.85	–*	
55–64.9 Gy	2.03 (0.27–14.80)	0.48		
≥65 Gy	1.69 (0.23–12.41)	0.60		

Data are presented as hazard ratio (95% confidence interval). *dropped out of the final multivariate model. S-PORT, time interval between surgery and initiation of postoperative radiotherapy; PORT, postoperative radiotherapy

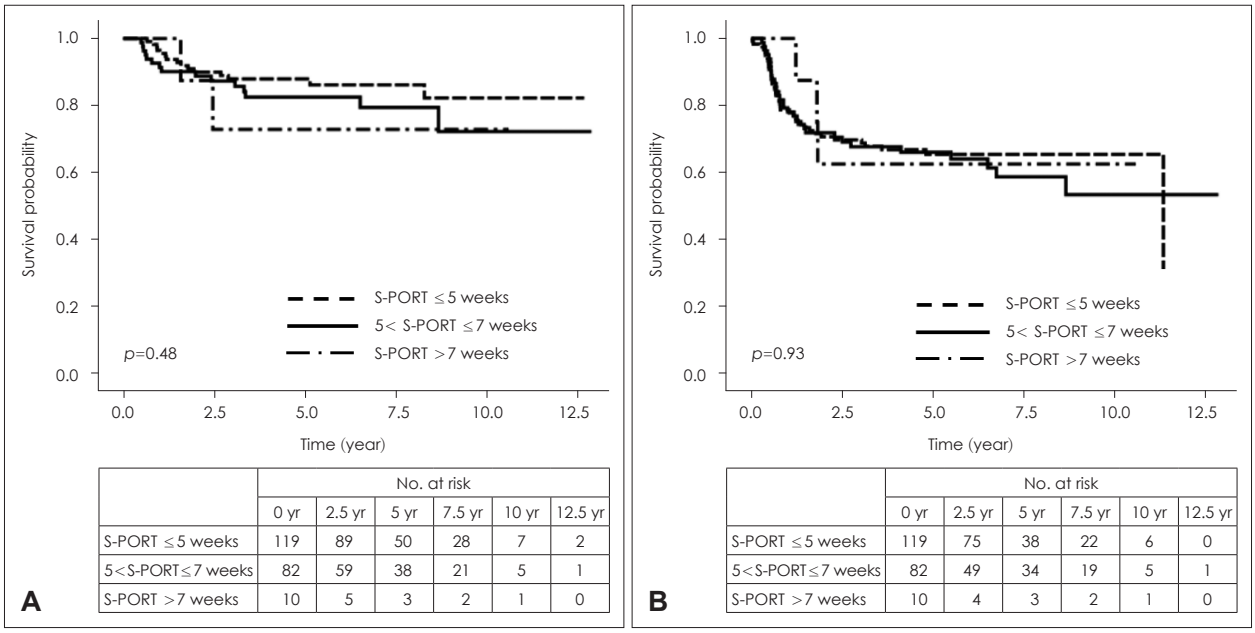


Fig. 3. Kaplan–Meier curves of overall survival (A) and progression-free survival (B) for the groups of S-PORT ≤5, 5–7, and >7 weeks. S-PORT, time interval between surgery and the initiation of postoperative radiotherapy.

performing pairwise comparison, there were also no statistical difference between the groups of S-PORT ≤5 vs. 5−7 weeks (OS, p=0.28; PFS, p=0.81), >7 vs. 5−7 weeks (OS, p=0.81; PFS, p=0.73), and ≤5 vs. >7 weeks (OS, p=0.42; PFS, p=0.86) in either OS or PFS (Fig. 3).

Discussion

This study evaluated the impact of delayed S-PORT >6 weeks on OS and PFS in patients who underwent curative-intent surgery and PORT for head and neck cancer. The results of this study confirmed that the OS and PFS of patients with S-PORT >6 weeks were not statistically different from those of patients with S-PORT ≤6 weeks. Furthermore, there was no statistical benefit of earlier S-PORT <5 weeks in comparison with S-PORT at approximately 6 weeks in terms of OS and PFS. Similarly, there was no statistically worse survival of patients with prolonged S-PORT >7 weeks in comparison with that of patients with S-PORT at approximately 6 weeks in terms of OS and PFS. The aforementioned results are contrary to the NCCN guidelines, which stipulate that PORT should be performed within 6 weeks after surgery to predict optimal oncologic outcomes.

Studies contrary to the NCCN guidelines in terms of S-PORT have been consistently published in the past.[5,6,11-13] A recent study published in 2017 of 4868 patients with oral cavity cancer enrolled in the National Cancer Database found that there was no significant OS difference in patients with S-PORT ≤6 weeks vs. S-PORT >64 days.[7] Instead, prolonged PORT duration was significantly associated with decreased OS. Similarly, another single-institution retrospective study published in 2019 of 277 patients diagnosed with oropharynx, larynx, hypopharynx, or oral cavity cancer found that prolonged S-PORT >67 days was not associated with a higher risk of locoregional recurrence.[14] Instead, prolonged radiation treatment time >43 days was associated with a higher risk of locoregional recurrence. A retrospective single-institution study of 180 patients with salivary gland cancer was also published in 2021 and demonstrated that there was no statistical difference in either OS or locoregional recurrence-free survival when stratifying S-PORT into quartiles (Q1, 8−47; Q2, 48−61; Q3, 62−72; Q4, 73−121 days).[15] Moreover, it demonstrated no significant difference in survival outcomes between patients with S-PORT <6 and ≥6 weeks in a multivariate model. However, a study having different threshold of S-PORT other than 6 weeks found that S-PORT >60 days in patients with oral cavity and oropharyngeal cancer resulted in impaired OS.[16] The reason why the outcomes of delayed S-PORT on survival rate were different may probably be the recent development of head and neck surgical technique and more sophisticated radiotherapy and chemotherapy, thereby reducing the relative effect of the current guideline of timely

initiation of PORT on survival. Instead, other factors have been further emphasized. For example, Schiff, et al.[11] found that S-PORT >6 weeks did not negatively impact locoregional control if administered with the appropriate tumoricidal dose of radiation. In addition, the total treatment time from surgery through the completion of PORT rather than S-PORT has also been emphasized as an important timely factor in head and neck cancer care.[17-19] However, its association with survival is still debatable owing to significant heterogeneity in defining the total treatment time. Diagnosis to treatment initiation has been one of the most widely investigated factors, and one of the studies published in 2019 found that delay in time to treatment initiation was associated with decreased OS.[20] However, delay thresholds varied from 20 to 120 days due to variation in defining delay and its association with survival according to other studies.[21]

In this study, 85.3% of the patients started PORT within 6 weeks, and only 4.7% of them failed to initiate PORT within 7 weeks postoperatively. However, according to the previous studies reporting a significant association of delayed S-PORT >6 weeks with decreased survival, more than 50% of the patients failed to initiate PORT within 6 weeks postoperatively.[9,22,23] Approximately 30% of the patients had an interval of S-PORT >8 weeks, which was a far larger number of patients than that of our study. Despite recent advances in radiotherapy, such as intensity-modulated radiotherapy, seriously prolonged S-PORT can affect patients with accelerated cell proliferation tumors due to the fact that the doubling time and tumor growth rate are directly related to the locoregional control of head and neck cancer.[4,24] Therefore, one of the possible reasons for the lack of statistical difference in survival between groups with S-PORT ≤6 and >6 weeks in our study could be that most of the patients with S-PORT >6 weeks initiated PORT not far exceeding 6 weeks compared with other studies. In addition, the higher 5-year OS rate was also thought to have reduced the negative effects of S-PORT >6 weeks in our study. In our study, the 5-year OS rates in the groups of S-PORT ≤6 and >6 weeks were 86.3% and 72.9%, which were higher than 70.8% and 60.2%, respectively, in a study by Graboyes, et al.[22] Similarly, according to the study of Ho, et al.,[9] the estimated 5-year OS rates for the S-PORT <40, 40–70, and >70 days were 66.5%, 56.8%, and 50.0%, respectively, which were lower than the 5-year OS rates in our study, although a direct comparison cannot be possible. As many studies investigating the association of S-PORT with survival have used cancer registry data, patient-specific details were not available despite the large database. Thus, there may be significant undisclosed heterogeneity during the course of treatment. However, patients in our study were more likely to receive consistent timely care from diagnosis to completion of treatment according to a relatively set schedule because only patients from two tertiary hospitals affiliated with the Korea University Medical Center were selected. These factors may explain the differences in survival rates between our study and previous studies.

This study has some limitations. First, the causes of delay in PORT initiation were not completely identified because this study was retrospective. It is unknown whether the delays were due to the patient's personal reasons or related to the disease. According to multiple studies, disparities in access to medical care or socioeconomic status are the common causes of delay in treatment.[25-27] However, these causes may not be the case in our country because our country has relatively good access to medical care and most of the nation is benefited by the National Health Insurance. Second, this study did not consider delays in diagnosis, initiation of surgery, or total treatment time, all of which could have affected survival. If these factors are considered in future studies, it will be a more complete study. Third, this study had a small sample size; therefore, there was some numerical difference in the actual 5-year OS rates between the groups of S-PORT ≤6 and >6 weeks, although the difference was not statistically significant. However, the actual PFS rates for both groups of S-PORT ≤6 and >6 weeks were comparable. There has been an opinion suggesting that PFS is a more appropriate outcome when assessing the effect of S-PORT on oncologic outcome.[22] Due to the small sample size, subanalysis was also not performed according to the subsite of primary tumors or the presence of HPV infection. Lastly, the pathologic stage was only analyzed, and it is not known if delay in S-PORT resulted in upstaging of the tumor from its initial clinical stage.

This study found that the OS and PFS of patients with S-PORT >6 weeks were not statistically different from those of patients with S-PORT ≤6 weeks. It is premature to revise the time interval of 6 weeks in the NCCN guidelines solely based on the results of our study. However, as more studies with similar results to ours accumulate, we may have the opportunity to revise the cutoff values of the S-PORT interval considering the medical situation of each country. In the future, retrospective studies with more patients will be needed to further confirm our conclusion and be able to accurately determine the impact of S-PORT on oncologic outcomes.

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Author Contribution

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REFERENCES

1) Institute of Medicine (US) Committee on Quality of Health Care in America. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academies Press;2001.
2) Bolwell BJ, Khorana AA. Enhancing value for patients with cancer: Time to treatment as a surrogate for integrated cancer care. J Natl Compr Canc Netw 2016;14(1):115-6.
3) National Comprehensive Cancer Network. Head and Neck Cancers [online] [cited 2022 Nov 10]. Available from: http://www.nccn.org/.
4) Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003;21(3):555-63.
5) Rosenthal DI, Liu L, Lee JH, Vapiwala N, Chalian AA, Weinstein GS, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. Head Neck 2002;24(2):115-26.
6) Marshak G, Rakowsky E, Schachter J, Shvero J, Feinmesser R, Sulkes A, et al. Is the delay in starting postoperative radiotherapy a key factor in the outcome of advanced (T3 and T4) laryngeal cancer? Otolaryngol Head Neck Surg 2004;131(4):489-93.
7) Fujiwara RJ, Judson BL, Yarbrough WG, Husain Z, Mehra S. Treatment delays in oral cavity squamous cell carcinoma and association with survival. Head Neck 2017;39(4):639-46.
8) Franco R, de Matos LL, Kulcsar MAV, de Castro-Júnior G, Marta GN. Influence of time between surgery and postoperative radiation therapy and total treatment time in locoregional control of patients with head and neck cancer: A single center experience. Clinics (Sao Paulo) 2020;75:e1615.
9) Ho AS, Kim S, Tighiouart M, Mita A, Scher KS, Epstein JB, et al. Quantitative survival impact of composite treatment delays in head and neck cancer. Cancer 2018;124(15):3154-62.
10) Marshak G, Popovtzer A. Is there any significant reduction of patients' outcome following delay in commencing postoperative radiotherapy? Curr Opin Otolaryngol Head Neck Surg 2006;14(2):82-4.
11) Schiff PB, Harrison LB, Strong EW, Fass DE, Shah JP, Spiro R, et al. Impact of the time interval between surgery and postoperative radiation therapy on locoregional control in advanced head and neck cancer. J Surg Oncol 1990;43(4):203-8.
12) Bastit L, Blot E, Debourdeau P, Menard J, Bastit P, Le Fur R. Influence of the delay of adjuvant postoperative radiation therapy on relapse and survival in oropharyngeal and hypopharyngeal cancers. Int J Radiat Oncol Biol Phys 2001;49(1):139-46.
13) Suwinski R, Sowa A, Rutkowski T, Wydmanski J, Tarnawski R, Maciejewski B. Time factor in postoperative radiotherapy: A multivariate locoregional control analysis in 868 patients. Int J Radiat Oncol Biol Phys 2003;56(2):399-412.
14) Tumati V, Hoang L, Sumer BD, Truelson JM, Myers LL, Khan S, et al. Association between treatment delays and oncologic outcome in patients treated with surgery and radiotherapy for head and neck cancer. Head Neck 2019;41(2):315-21.
15) Romine PE, Voutsinas J, Wu V, Tratt M, Liao J, Parvathaneni U, et al. Timing of postoperative radiation therapy and survival in resected salivary gland cancers: Long-term results from a single institution. Oral Oncol 2021;123:105626.
16) Liederbach E, Lewis CM, Wang CH, Shaikh A, Bhavani MK. Impact of delays to adjuvant radiation therapy on survival in squamous cell carcinoma of the oral cavity and oropharynx. Oncology (Williston Park) 2015;29(4 Suppl 1):204937.
17) Shaikh T, Handorf EA, Murphy CT, Mehra R, Ridge JA, Galloway TJ. The impact of radiation treatment time on survival in patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2016;96(5):967-75.
18) Guttmann DM, Kobie J, Grover S, Lin A, Lukens JN, Mitra N, et al. National disparities in treatment package time for resected locally advanced head and neck cancer and impact on overall survival. Head Neck 2018;40(6):1147-55.
19) Chen MM, Harris JP, Orosco RK, Sirjani D, Hara W, Divi V. Association of time between surgery and adjuvant therapy with survival in oral cavity cancer. Otolaryngol Head Neck Surg 2018;158(6):1051-6.
20) Liao DZ, Schlecht NF, Rosenblatt G, Kinkhabwala CM, Leonard JA, Ference RS, et al. Association of delayed time to treatment initiation with overall survival and recurrence among patients with head and neck squamous cell carcinoma in an underserved urban population. JAMA Otolaryngol Head Neck Surg 2019;145(11):1001-9.
21) Graboyes EM, Kompelli AR, Neskey DM, Brennan E, Nguyen S, Sterba KR, et al. Association of treatment delays with survival for patients with head and neck cancer: A systematic review. JAMA Otolaryngol Head Neck Surg 2019;145(2):166-77.
22) Graboyes EM, Garrett-Mayer E, Ellis MA, Sharma AK, Wahlquist AE, Lentsch EJ, et al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. Cancer 2017;123(24):4841-50.
23) Cramer JD, Speedy SE, Ferris RL, Rademaker AW, Patel UA, Samant S. National evaluation of multidisciplinary quality metrics for head and neck cancer. Cancer 2017;123(22):4372-81.
24) Mackillop WJ, Bates JH, O'Sullivan B, Withers HR. The effect of delay in treatment on local control by radiotherapy. Int J Radiat Oncol Biol Phys 1996;34(1):243-50.
25) Albano JD, Ward E, Jemal A, Anderson R, Cokkinides VE, Murray T, et al. Cancer mortality in the United States by education level and race. J Natl Cancer Inst 2007;99(18):1384-94.
26) Shavers VL, Harlan LC, Winn D, Davis WW. Racial/ethnic patterns of care for cancers of the oral cavity, pharynx, larynx, sinuses, and salivary glands. Cancer Metastasis Rev 2003;22(1):25-38.
27) Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin 2004;54(2):78-93.