CANCER DIAGNOSIS & PROGNOSIS
4: 658-666 (2024) doi: 10.21873/cdp.10378

Interval to Recurrence Affects Survival in Recurrent Head and Neck Squamous Cell Carcinoma

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Abstract. *Background/Aim: Approximately half of head and neck squamous cell carcinoma (HNSCC) cases recur, with most recurrences occurring within the first two years after treatment. Although it has been suggested that the interval to recurrence after radical treatment is associated with prognosis in patients with HNSCC, further investigation is needed. Patients and Methods: Patients diagnosed with HNSCC at Kyushu University Hospital were retrospectively analyzed (n=500). Early recurrence (ER) was defined as disease recurrence within six months of radical treatment, whereas late recurrence (LR) was defined as recurrence after more than six months. Continuous variables were assessed using the Mann–Whitney U-test and categorical variables were assessed using Fisher's exact test. Results: A total of 234 patients experienced recurrence, with 110 and 124 patients experiencing ER (recurrence within two to six months) and LR (recurrence after six months), respectively. Multivariate analyses identified two independent risk factors for poor prognosis: ER [hazard ratio (HR)=3.200, 95% confidence interval (CI)=1.570-6.521, p=0.001] and absence of radiotherapy (HR=0.374, 95%CI=0.191-0.733, p=0.004). In patients with recurrent HNSCC, a short interval to recurrence is a risk factor for poor prognosis and survival. This study demonstrated the prognostic value of ER in these patients. Conclusion: The selection of treatment for patients with recurrent head and neck squamous cell carcinoma should consider the timing of recurrence, the initial treatment regimen, and the strategy for changing salvage therapy depending on the recurrence status.*

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Key Words: Interval to recurrence, head and neck squamous cell carcinoma, prognosis, radiotherapy, platinum resistance.

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world (1). For local HNSCCs without distant metastases, radical treatment (including surgical therapy, radiotherapy/chemoradiotherapy, or a combination of both) is preferred depending on the stage (1). However, given that locally advanced HNSCCs (LAHNSCCs) account for over 60% of local HNSCCs, approximately half of them recur (2, 3), and most of those recur within the first two years after treatment (4, 5).

Interestingly, the interval to recurrence after radical resection is associated with clinical outcomes in certain malignant tumors. In gastric- (6), liver- (7), pancreatic- (8), kidney- (9), and esophageal (10) cancers, early recurrence (ER) after radical resection has a poorer prognosis than late recurrence (LR). An association between recurrence timing and patient survival is reported in HNSCC (11-13); however, investigations are insufficient.

Additionally, HNSCC shares the concept of platinum resistance with ovarian cancer (14); recurrence within six months of platinum-based chemotherapy is defined as platinum-resistant cancer, and recurrence thereafter is defined as platinum-sensitive cancer (15). Platinum-resistant HNSCC has a poor prognosis (16). The initial treatment of patients with LAHNSCC includes chemotherapy in combination with radiotherapy or surgery. In other words, it is difficult to determine whether patients with recurrence within six months are truly resistant to platinum preparations or are actually resistant to radiotherapy.

The primary purpose of our study was to explore the relationship between recurrence time and overall survival (OS) in patients with HNSCC. The second purpose was to analyze platinum and radiotherapy resistance, together with

survival outcomes in HNSCC, and identify the risk factors for poor prognosis in patients with recurrent HNSCC.

Patients and Methods

Patient cohort. We retrospectively collected and analyzed the data of 643 patients who had HNSCC without distant metastasis at the time of initial treatment and received radical treatment at Kyushu University Hospital between January 1, 2015, and December 31, 2021.

The exclusion criteria were as follows: recurrence was defined as the appearance of a new lesion six weeks after the disappearance of lesions following radical treatment (17) and patients in whom new lesions appeared within less than six weeks (n=4) were excluded from the analysis as residuals. Patients with heterochronic occurrence of a multiplicity of cancers in the head and neck area (n=105) were also excluded from the analysis owing to the unknown origin of the recurrence. Patients who could not be followed up for over two years (n=34) were also excluded from the analysis. Finally, 500 patients were included in this study. The patient observation period was until death or December 31, 2023, and the median follow-up period was 40 months (range=4-293 months).

This study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Review Board of Kyushu University (No. 2022-27). Informed consent was mostly obtained in writing, and some patients were granted the opportunity to refuse participation by opting out on the institution's website.

Definitions. Early recurrence was defined as disease recurrence within six months of radical treatment, whereas LR was defined as recurrence after more than six months. Additionally, platinum-resistant patients were defined as patients who showed recurrence within six months of platinum preparation use, as previously reported (14, 15), and radiation-resistant patients were those in whom lesions disappeared after the completion of radiotherapy but had recurred within six months.

The tumor–node–metastasis classification was based on the Union for International Cancer Control classification (8th edition). Overall survival was defined as the period from initial treatment to death.

Statistical analysis. For the statistical significance test, continuous variables were assessed using the Mann–Whitney *U*-test, and categorical variables were assessed using Fisher's exact test. Overall survival was calculated using the Kaplan–Meier method and was compared using the log-rank test. Clinicopathological factors that might affect OS were identified using univariate and multivariate Cox proportional hazards models. Risk was expressed as the hazard ratio (HR), and the 95% confidence interval (CI) was determined using the reference groups. The SPSS Statistics software program ver. 22.0 (IBM Japan, Ltd., Tokyo, Japan) was used for all statistical analyses, and a p-value <0.05 was considered statistically significant.

Results

Patient characteristics. The patients' baseline characteristics are shown in Table I. Among the 500 patients, 377 (75.4%) were male, and 123 (24.6%) were female. The median patient age was 67 years (range=20-92 years). The most common cancer site was the oral cavity [145 patients (29.0%)], followed by the hypopharynx [113 patients (22.6%)]. According to the T classification, T1/T2 accounted for 246 patients (49.2%), whereas T3/T4 accounted for 254 patients (50.2%). Additionally, N0 was the most common N classification with 252 patients (50.4%).

A total of 302 patients (60.4%) underwent surgery for initial treatment, among whom radiotherapy with or without chemotherapy was administered after surgery in 126 patients who were extracapsular spread-positive (18, 19) and margin-positive (18, 19). These were considered risk factors for poor prognosis, with radiotherapy alone in 28 patients, cisplatin combination (100 mg/m^2, triweekly) in 87 patients, and TS-1 combination (100 mg/body/day) in 11 patients. Additionally, neoadjuvant chemotherapy (60 mg/m^2 docetaxel on day 1, 60 mg/m^2 cisplatin on day 1, 600 mg/m^2 5FU on days 1-4) was administered to 19 patients. Radiotherapy or chemoradiotherapy was administered to 198 patients (39.6%) as the initial treatment with radiotherapy or chemoradiotherapy alone, cisplatin combination (100 mg/m^2, triweekly), and TS-1 combination (100 mg/body/day) for 17, 147, and 34 patients, respectively. Platinum preparations were used for chemoradiotherapy or neoadjuvant chemotherapy at initial treatment in 253 patients (50.6%).

Among the patients who underwent surgery, the margin status was assessed in 297 patients, out of which 115 (38.7%) were margin-positive. Lymph nodes were dissected in 202 patients, 47 (23.3%) of whom had extracapsular spread. Additionally, perineural invasion (pn), lymph vessel invasion (ly), and blood vessel invasion (v) were assessed in 288 patients, and 94 (32.6%) tested positive for one or more.

Overall survival by recurrence status. Among the 500 patients who received the initial treatment, 234 (46.8%) experienced recurrence during the observation period. A total of 110 patients had ER (22.0%), and 124 patients had LR (24.8%), with 110 patients (22.0%) showing recurrence at two to six months, 59 patients (11.8%) at 7-12 months, 31 patients (6.2%) at 13-24 months, and 34 patients (6.8%) after 25 months (Figure 1).

The characteristics of the patients with ER (recurrence within six months) and LR (recurrence after six months) are shown in Table I. Among patients with LR, the percentage of nasopharyngeal and laryngeal cancers was higher (p=0.014); there were more patients with T1 (p=0.003), and fewer patients were positive for pn, ly, or v (p=0.002). However, no significant difference was observed in history of radiotherapy and platinum use. The ER group had a significantly worse OS than the LR group (Figure 2, p<0.001).

Survival rate by resistance to platinum preparation and radiotherapy. Among the 253 patients who used a platinum preparation at the initial treatment, 52/253 (20.6%) had platinum-resistant recurrence, whereas 54/253 (21.3%) had

Table I. *Baseline characteristics of all patients (n=500).*

		All (n=500)	Recurrence (n=234)		*p*-Value
			ER (n=110)	LR (n=124)	
Sex	Male	377	80	96	0.450 (F)
	Female	123	30	28	
Age (years), mean (SD)	Median	20-92 (67)	33-92 (65)	20-86 (66)	0.995 (M)
Area	Oral cavity	145	51	33	0.014 (F)
	Nasopharynx	21	2	7	
	Oropharynx	79	15	16	
	Hypopharynx	113	20	32	
	Larynx	64	7	20	
	Nasal sinus	41	9	12	
	External auditory canal	37	6	4	
T classification	T1	84	9	23	0.003 (M)
	T2	162	32	41	
	T3	112	20	26	
	T4	142	49	34	
N classification	N0	252	44	59	0.370 (M)
	N1	74	16	12	
	N2	155	43	47	
	N3	19	7	6	
P16	Positive	48	7	7	0.736 (F)
	Negative	43	12	10	
	Unmeasured	409	91	107	
Initial treatment	Surgery alone	157	30	41	0.103 (F)
	+ Chemoradiotherapy (platinum+)	87	29	17	
	+ Radiotherapy (platinum–)	39	12	11	
	+ Neoadjuvant chemotherapy (platinum+)	19	5	3	
	Radiotherapy alone	17	5	4	
	Chemoradiotherapy (platinum+)	147	21	29	
	Chemoradiotherapy (platinum–)	34	8	19	
Postoperative pathological findings of the surgical therapy group	Non-surgery group	198	34	52	0.103 (F)
	Surgery group	302	76	72	
	Margin				
	Positive	115	35	30	
	Negative	182	39	38	0.795 (F)
	Unknown	5	2	3	
	Extracapsular spread				
	Yes	47	24	8	
	No	67	21	20	
	p0	88	15	13	0.091 (F)
	pn, ly, v				
	Yes	94	42	19	
	No	194	29	45	
	Unknown	10	4	4	0.002 (F)
Multiplicity cancer in other organs	No	394	93	98	0.313 (F)
	Yes	106	17	26	

F: Fisher's exact test; M: Mann–Whitney *U*-test; ER: early recurrence; LR: late recurrence; SD: standard deviation; pn: perineural invasion; ly: lymph vessel invasion; v: blood vessel invasion.

platinum-sensitive recurrence. The platinum-resistant group had a significantly poorer prognosis than the platinum-sensitive group (Figure 3A, p=0.026).

Among the 324 patients who received radiotherapy at initial treatment (including after surgery), 75/324 (23.1%) had radiotherapy-resistant recurrence, whereas 80/324 (24.7%) had radiotherapy-sensitive recurrence. The radiotherapy-resistant group had a significantly worse prognosis than the radiotherapy-sensitive group (Figure 3B, p=0.003).

Survival rate by pathological findings of surgery patients. Patients who were margin-positive (n=115) had a significantly

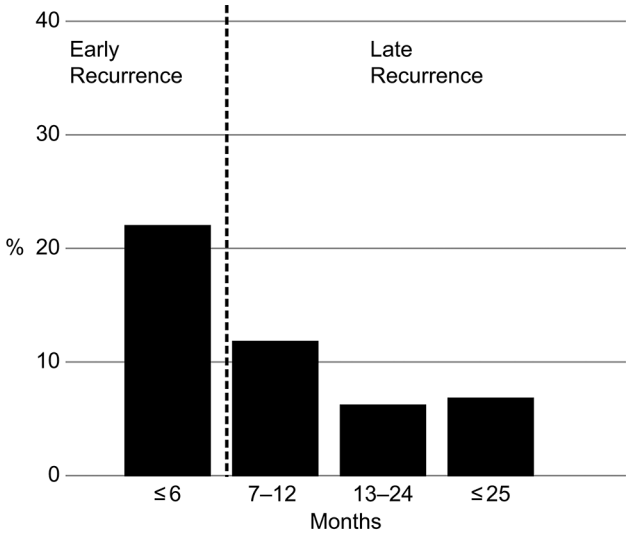

Figure 1. *Recurrence time and frequency. In total, 46.8% of patients with HNSCC experienced recurrence. Early recurrence accounted for 22.0% of cases, and late recurrence for 24.8%.*

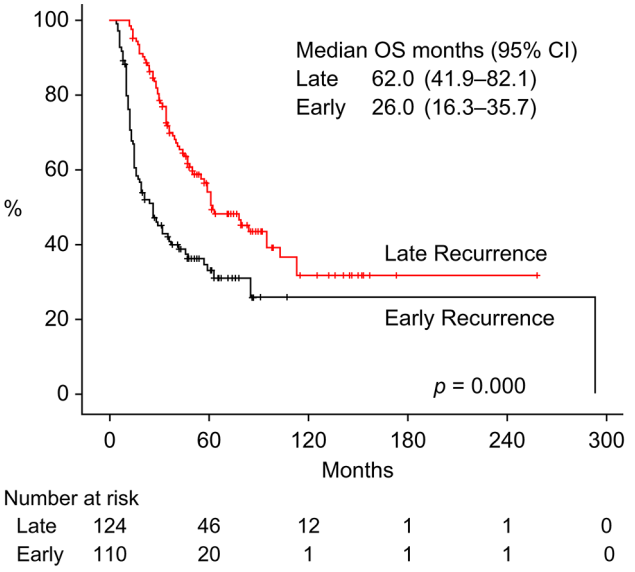

Figure 2. *Survival curves for early recurrence (recurrence within two to six months) and late recurrence (recurrence after six months). OS: Overall survival; CI: confidence interval.*

worse prognosis than patients who were margin-negative (n=182) (Figure 4A, p=0.023). Patients with lymph node extracapsular spread (n=47) had a significantly worse prognosis than patients without extracapsular spread (n=67) and with pN0 (n=88) (Figure 4B, p=0.000). Additionally, patients who were positive for pn, ly, or v (n=94) had a significantly worse prognosis than patients who were negative for these factors (n=194) (Figure 4C, p=0.000).

Predictors of outcome. Multivariate analyses revealed that the independent risk factors for poor prognosis were ER in LAHNSCC (HR=3.200, 95%CI=1.570-6.521, p=0.001) and no radiotherapy (HR=0.374, 95%CI=0.191-0.733, p=0.004) (Table II). Platinum resistance, platinum sensitivity, radiation resistance, or radiation sensitivity were not significant prognostic factors.

Discussion

In this retrospective study, 46.8% of patients who received surgical therapy or radiotherapy/chemoradiotherapy for curative purposes experienced recurrence, and approximately half of the patients with recurrence experienced it within six months. This result is similar to that of a previous study (20). Additionally, this study demonstrated that recurrence-free interval affects prognosis. This is one of the few studies reporting that interval to recurrence is a prognostic factor for survival in patients with recurrent HNSCC after treatment with various modalities.

Previous studies demonstrating the association between the interval to recurrence and clinical outcomes mainly arose after recurrence following radical resection was observed in other carcinomas (6-10) and HNSCC (12, 21). In all reports, patients with ER had a significantly worse prognosis than those with LR. Additionally, few studies demonstrate an association between the interval to recurrence after radiotherapy for HNSCC and clinical outcomes. According to these studies, a short interval to salvage surgery after radiotherapy for HNSCC is a significant negative prognostic factor (22, 23). To the best of our knowledge, only three reports have investigated the association between recurrence after initial treatment (including all treatment modalities) and prognosis, like the present study (11, 20, 24). Among them, two previous studies defined cases with a recurrence-free interval of less than 12 months as ER, whereas the remaining study defined recurrence within six months or less than as ER, which is similar to our definition. All three studies concluded that a longer recurrence-free interval leads to a better prognosis. In the current study, we defined ER as recurrence within six months because of doubts regarding the concept of platinum resistance, which is widely used in head and neck cancer treatment. For the investigation of the association between interval to HNSCC recurrence and prognosis, we also examined whether patients who showed recurrence within six months after platinum use were only resistant to platinum or if they were originally resistant to any treatment modality. The results of this study indicate that the prognosis is poor for patients with ER regardless of the treatment modality; thus, it was suggested that the prognosis may have little to do with whether the tumor is truly platinum resistant or sensitive. This shows that there are doubts about

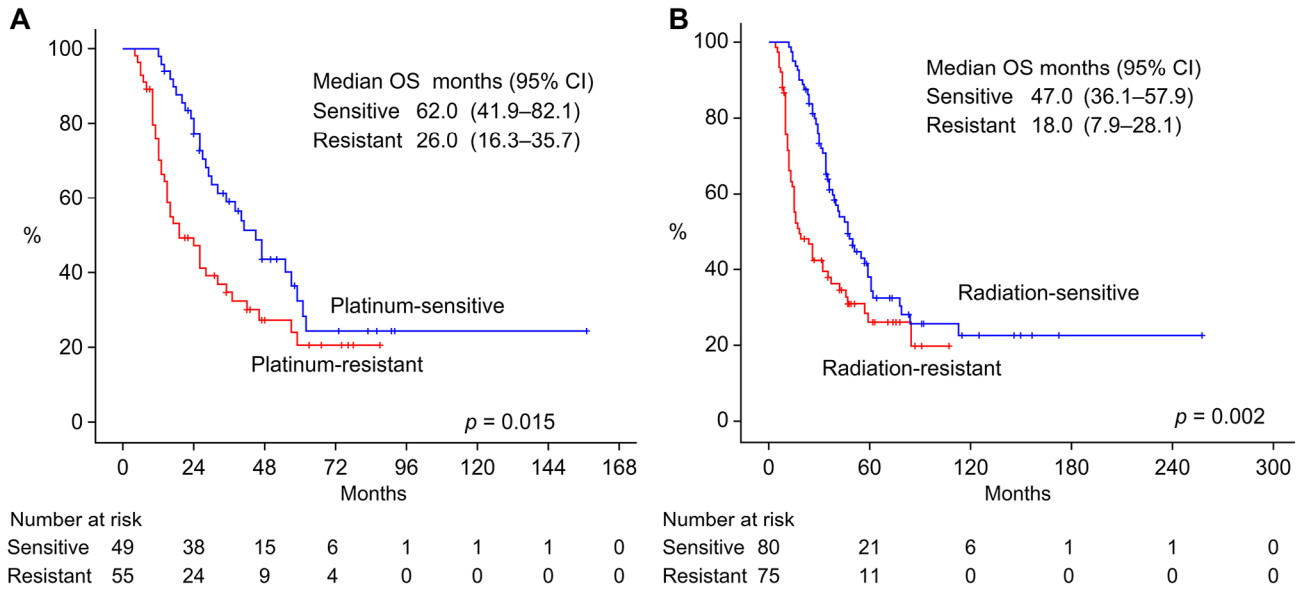

Figure 3. *Survival curves for patients treated with platinum or radiotherapy (A) Survival curves for platinum-resistant and platinum-sensitive recurrence. (B) Survival curves for radiotherapy-resistant recurrence (recurrence in two to six months) and radiotherapy-sensitive recurrence (recurrence after six months). OS: Overall survival; CI: confidence interval.*

Table II. *Univariate and multivariate analyses of variables for overall survival (OS) in patients with recurrence (n=234).*

Variables		OS univariate analysis HR (95%CI), *p*-Value	OS multivariate analysis HR (95%CI), *p*-Value
Recurrence time	ER: recurrence two to six months after treatment (n=110)	2.126 (1.509-2.995),	3.200 (1.570-6.521)
	LR: recurrence over six months after treatment (n=124)	***p*=0.000** Ref	***p*=0.001** Ref
Radiotherapy	Recurrence two to six months after radiotherapy (n=75)	1.824 (1.237-2.690),	0.567 (0.232-1.390)
		***p*=0.002** Ref	*p*=0.215 Ref
	Recurrence over six months after treatment (n=80)	0.593 (0.382-0.923),	0.374 (0.191-0.733)
		***p*=0.021**	***p*=0.004**
	Recurrence without treatment (n=79)		
Platinum preparation	Platinum-resistant recurrence (n=52)	1.721 (1.078-2.747),	0.998 (0.501-1.988),
		***p*=0.023** Ref	*p*=0.995 Ref
	Platinum-sensitive recurrence (n=54)	0.737 (0.488-1.114),	0.881 (0.535-1.452)
		p=0.148 Ref	*p*=0.619
	Recurrence without platinum administration (n=128)		
Multiplicity cancer in other organs	No (n=191)	Ref	–
	Yes (n=43)	1.387 (0.929, 2.071), *p*=0.110	

HR: Hazard ratio; CI: confidence interval; ER: early recurrence; LR: late recurrence; Ref: reference. Significant *p*-values are indicated in bold.

whether the concept of platinum resistance/sensitivity in the head and neck area captures the true nature of tumors.

Early recurrence is mainly due to the aggressive biological behavior of the tumors themselves, such as rapid growth rate and treatment resistance (22). A study of patients who underwent chemoradiotherapy after surgery reported that patients with very ER, in whom macroscopic tumors recurred while waiting for radiotherapy, accounted for approximately 20% of all patients, and such patients had a poor prognosis (25). However, an accurate mechanism for poor prognosis in

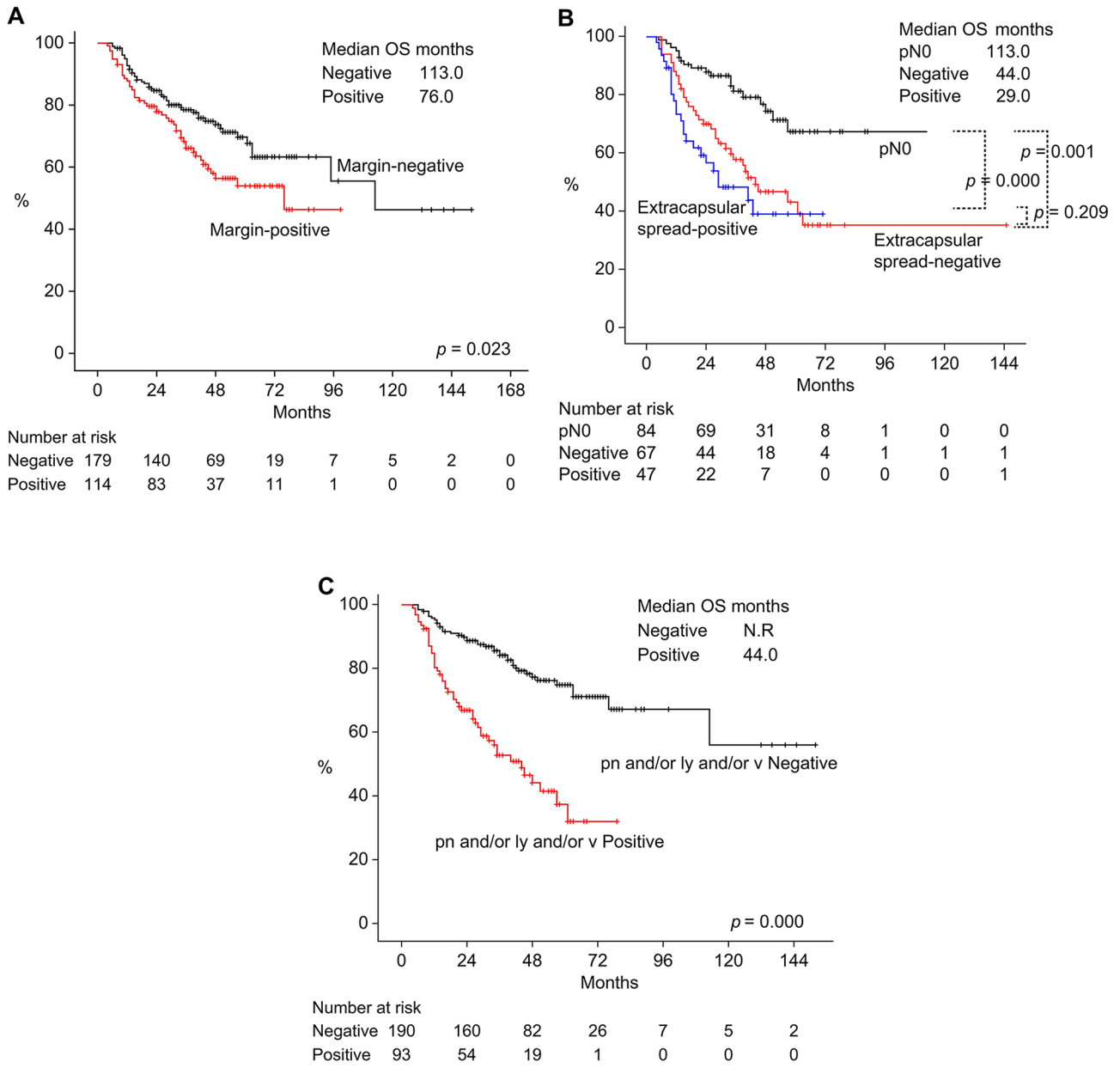

Figure 4. *Survival curves based on postoperative pathology (A) Survival curves for patients who were margin-positive and margin-negative. (B) Survival curves for patients with and without extracapsular spread and with pN0. (C) Survival curves for patients who were positive for either pn, ly, or v, and those who were negative for all three. OS: Overall survival; N.R.: not reached; pn: perineural invasion; ly: lymph vessel invasion; v: blood vessel invasion.*

patients with ER has not been demonstrated. Some genomic and proteomic analyses show the possibility of identifying poor prognoses, but they are still in the research phase (26, 27). For this reason, the identification and selection of patients with ER before treatment remains challenging. Additionally, preventive measures are difficult even if patients are identified. This study also demonstrated the difficulties in improving the OS of patients with a poor prognosis. Notably, all positive patients among the patients undergoing surgery had a poor prognosis, even though many who were extracapsular spread-positive (18, 19), margin-positive (18, 19), and pn/ly/v-positive (19) (which are considered risk factors for poor prognosis) underwent postoperative radiotherapy or chemoradiotherapy. This shows that it is difficult to completely eliminate the poor prognostic environment as a tumor factor even if multimodal treatment involving surgery, radiotherapy, and chemotherapy is performed.

To overcome this difficulty, trials involving preoperative immunotherapy using immune checkpoint inhibitors and their use as maintenance therapy after chemoradiotherapy or surgery, as new strategies to improve OS, are currently underway, and results are anticipated. Additionally, given the results of this study, we propose a treatment strategy based on a different approach for patients with recurrence. Currently, when selecting treatment for patients with recurrence, it is recommended to devise treatment strategies (28) that are based on the recurrence site, initial treatment content, and combined positive score before immune checkpoint inhibitor use (29). However, we conclude that changing salvage therapy depending on the recurrence status could also be a good strategy. Notably, depending on the time to relapse, treatment strategies differ in patients with small cell lung cancer. These patients are divided into two groups: the sensitive relapse group, which responds to initial chemotherapy and has a long interval before relapse, and the refractory relapse group, which has a short interval before relapse (30, 31). Using similar measures for HNSCC may improve the prognosis of patients with ER.

The strength of this study is the addition of the perspective of resistance to platinum preparations and radiotherapy at the time of recurrence as factors that may affect OS. Multivariate analyses revealed that ER status, rather than resistance to platinum preparations or radiotherapy, affected OS. However, this study has several limitations. First, this was a retrospective study, and the limitations and risks of selection bias could not be eliminated. Second, the survey results cannot be generalized to different populations. Third, the prognostic factors to be subjected to multivariate analyses were limited by the sample size. For example, several factors that may affect the recurrence risk and prognosis of patients with HNSCC (such as resection margin; extracapsular spread; ly, pn, and v; and human papillomavirus status) could not be included owing to sample size limitations. It is necessary to increase the sample size to include all prognostic predictors in future studies. This will help obtain more accurate estimates of recurrence risk.

Conclusion

After treatment with various modalities, approximately half of the patients with recurrent HNSCC experienced recurrence during the observation period. Furthermore, half of the patients showed recurrence within two to six months. Interval to recurrence is a significant independent prognostic risk factor for OS. This study demonstrated the prognosis of patients with ER. Early recurrence cases should be considered for different treatment strategies (*e.g.*, addition of drugs) rather than LR cases owing to the presumed poor prognosis.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Mioko Matsuo: Writing – original draft, Conceptualization, Methodology, Investigation. Kazuki Hashimoto: Validation. Ryunosuke Kogo: Resources. Masanobu Sato: Data curation. Tomomi Manako: Data curation. Takashi Nakagawa: Supervision.

Acknowledgements

The Authors thank Editage (www.editage.jp) for English language editing.

Funding

This research received no external funding.

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Received June 3, 2024
Revised July 11, 2024
Accepted July 12, 2024