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

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Article

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Simple Summary: Head and neck squamous cell carcinomas are often locally advanced, and approximately half of them recur even after surgery or radiotherapy with platinum drugs. It has been suggested that the interval between recurrence and recurrence may be related to prognosis. The purpose of this study was to determine whether the time to recurrence and prognosis were due to the initial treatment or the intrinsic tumor characteristics. Results showed that a short interval to recurrence (within six months) was an independent poor prognostic factor for survival. We propose a strategy of enhanced rescue therapy for patients with recurrence within six months.

Abstract: Approximately half of head and neck squamous cell carcinoma (HNSCC) cases recur, and most of them recur within the first two years after treatment. Although it has been suggested that the interval to recurrence after radical treatment and prognosis in patients with HNSCC are associated, investigations are insufficient. In this study, patients diagnosed with HNSCC at Kyushu University Hospital were retrospectively analyzed (n = 500). A total of 234 patients experienced recurrence, with 110 and 124 patients experiencing early recurrence (ER) (recurrence within 2–6 months) and late recurrence (LR) (recurrence after 7 months), respectively. There were two independent risk factors for poor prognosis in the multivariate analyses: ER (hazard ratio [HR] = 3.200, 95% confidence interval [CI] = 1.570–6.521, p = 0.001) and no 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 patients. During the selection of treatment for patients with recurrence, the recurrent area, initial treatment content, and strategy of changing salvage therapy depending on the recurrence status should be considered.

Keywords: squamous cell carcinoma; recurrence; radiotherapy

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world [1]. For local HNSCCs (LHNSCCs) 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 more than 60% of LHNSCCs, approximately half of them recur subsequently [2,3], and most of them recur within the first two years after treatment [4,5].

Interestingly, the interval to recurrence after radical resection has been reported to be 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). Even in HNSCC, an association between recurrence timing and patient survival has been reported [11-13]; however, investigations are insufficient.

In addition, HNSCC shares the concept of platinum resistance with ovarian cancer [14]; recurrence within six months of platinum-based chemotherapy is defined as platinum-resistive

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cancer, and recurrence after that is defined as platinum-sensitive cancer [15]. Platinum-resistive HNSCC is known to have a poor prognosis [16]. For the initial treatment of LAHNSCC, none of the patients were treated with chemotherapy alone but underwent chemotherapy in combination with radiotherapy or surgery. In other words, in HNSCC based on radiotherapy in combination with platinum preparations as the radical treatment, it is difficult to distinguish 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, as well as survival outcomes in HNSCC, and identify the risk factors for poor prognosis in patients with recurrent HNSCC.

2. Materials and Methods

2.1. 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 lesions appeared in 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 because of the unknown origin of the recurrence. Patients who could not be followed up for more than 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).

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. 22301-00). 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.

2.2. Definitions

ER was defined as disease recurrence within six months of radical treatment, whereas LR was defined as recurrence after more than six months. In addition, platinum-resistive patients, as previously reported [14,15], were defined as patients who showed recurrence within six months of platinum preparation use, 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). OS was defined as the period from initial treatment to death.

2.3. 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. OS 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 hazard ratio (HR) and the 95% confidence interval (CI) was determined using the reference groups. For statistical analysis, the SPSS Statistics software program ver. 22.0 (IBM Japan, Ltd., Tokyo, Japan) was used in all tests, and a $p < 0.05$ was considered statistically significant.

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3. Results

3.1. Patient Characteristics

The patients' baseline characteristics are shown in Table 1. 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). 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%). In addition, according to N classification, N0 was the most common with 252 patients (50.4%).

Table 1. Baseline Characteristics of All Patients (n = 500).

		All (n = 500)	Recurrence (n = 234)		*p* value
			ER (n = 110)	LR (n = 124)	
Gender	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	0.795 (F)
	Negative	182	39	38	
	Unknown	5	2	3	
	Extracapsular spread Yes	47	24	8	0.091 (F)
	No	67	21	20	

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	p0	88	15	13	
	pn, ly, vn Yes	94	42	19	0.002 (F)
	No	194	29	45	
	Unknown	10	4	4	
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.

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. In addition, neoadjuvant chemotherapy (docetaxel 60 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 1, 5FU 600 mg/m^2 days 1–4) was performed on 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 found to be margin positive. Lymph nodes were dissected in 202 patients, 47 (23.3%) of whom had extracapsular spread. In addition, perineural invasion (pn), lymph vessel invasion (ly), and blood vessel invasion (v) were assessed in 288 patients, and 94 (32.6%) tested positive for either of them.

3.2. OS 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 2–6 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).

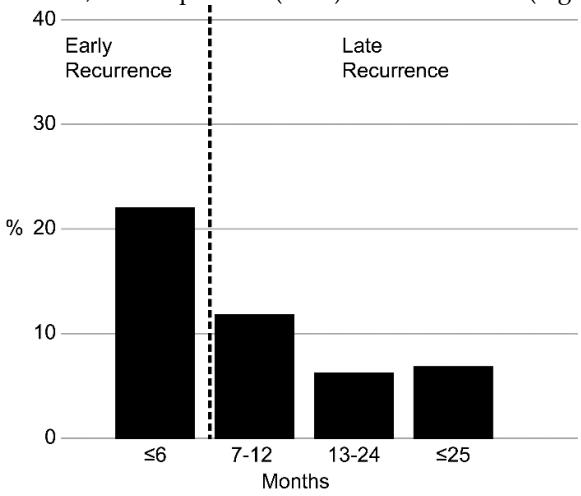

Figure 1. Recurrence time and frequency.

The characteristics of the patients with ER (recurrence within six months) and LR (recurrence in more than six months) are shown in Table 1. Among patients with LR, the percentage of nasopharyngeal and laryngeal cancers was higher (p = 0.014); there were more patients with T1 (p =

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0.003); and fewer patients were positive for either pn, ly, or v (p = 0.002). However, no significant difference was observed in radiotherapy and platinum use histories.

The OS curves of the ER and LR groups are shown (Figure 2). The ER group had a significantly worse prognosis than the LR group (p < 0.001).

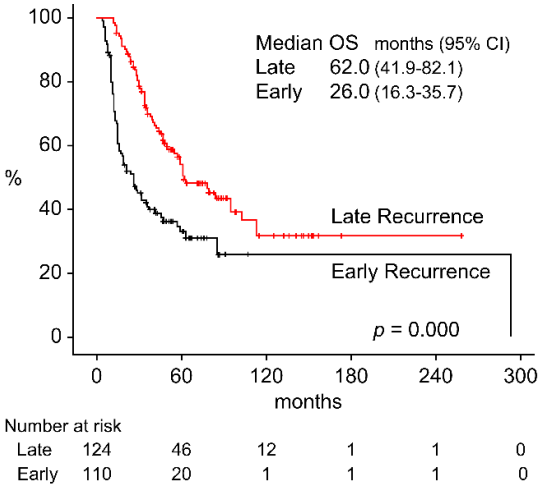

Figure 2. Survival curves for ER (recurrence in two to six months) and LR (recurrence after seven months).

3.3. Survival Rate by Resistance to Platinum Preparation and Radiotherapy

Among the 253 patients who used a platinum preparation at the initial treatment, 52 (20.6%, 52/253) had platinum-resistant recurrence, whereas 54 (21.3%, 54/253) had platinum-sensitive recurrence. The platinum-resistive group had a significantly poorer prognosis than the platinum-sensitive group (p = 0.026, Figure 3-a).

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

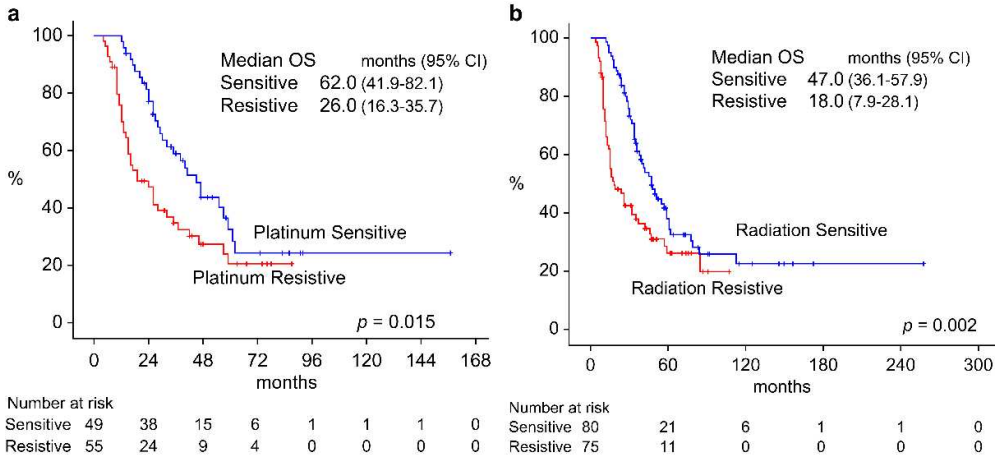

Figure 3. (a) Survival curves for platinum-resistive recurrence and platinum-sensitive recurrence. **(b)** Survival curves for radiotherapy-resistive recurrence (recurrence in two to six months) and radiotherapy-sensitive recurrence (recurrence after seven months).

3.4. Survival Rate by Pathological Findings of Surgery Patients

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Patients who were margin positive (n = 115) had a significantly worse prognosis than patients who were margin negative (n = 182) (p = 0.023, Figure 4-a).

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) (p = 0.000, Figure 4-b).

In addition, patients who were positive for perineural invasion (pn), lymph vessel invasion (ly), or blood vessel invasion (v) (n = 94) had a significantly worse prognosis than patients who were negative for these factors (n = 194) (p = 0.000, Figure 4-c).

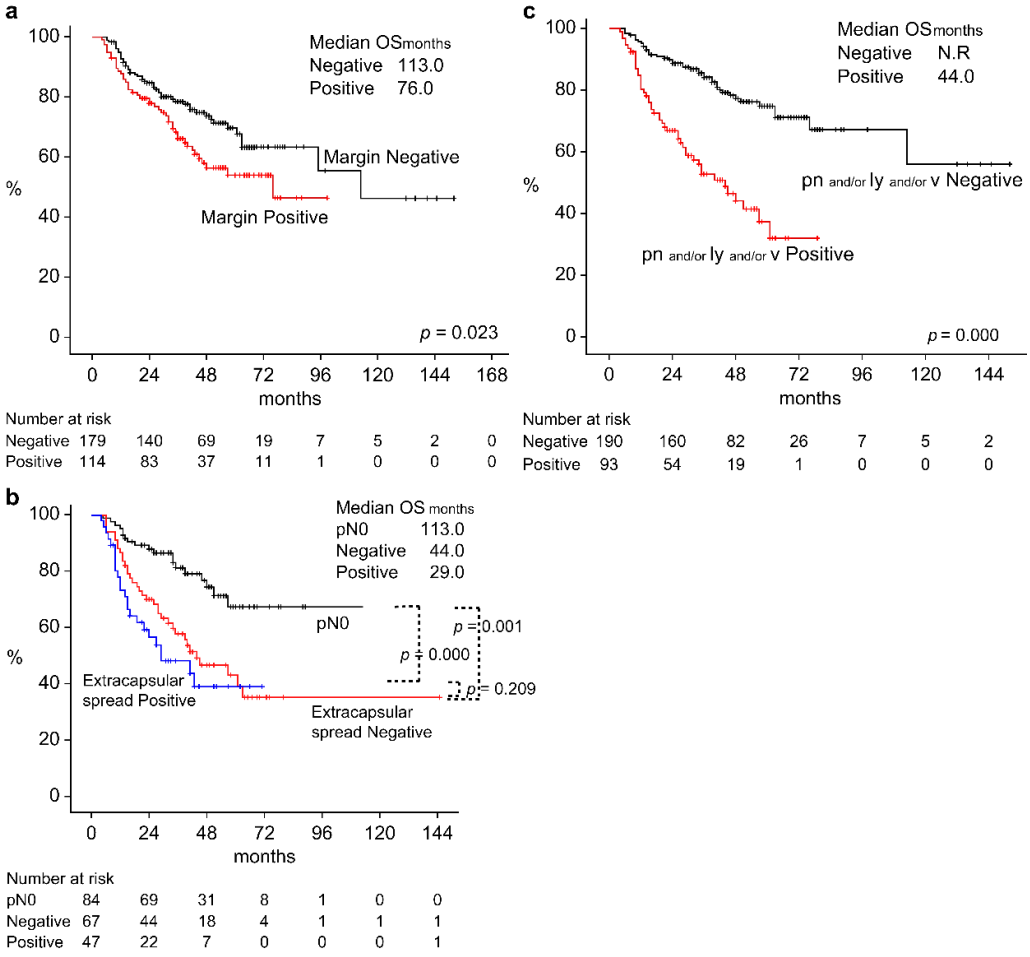

Figure 4. (a) Survival curves for patients who were margin positive and margin negative. **(b)** Survival curves for patients with and without extracapsular spread and had pN0. **(c)** Survival curves for patients who were positive for either pn, ly, or v and patients who were negative for all of pn, ly, and v.

3.5. Predictors of Outcomes

The results of the univariate and multivariate analyses predicting OS are summarized in Table 2. Multivariate analyses revealed that in LAHNSCC, the independent risk factors for poor prognosis were ER (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). Platinum resistance, platinum sensitivity, radiation resistance, or radiation sensitivity were not significant prognostic factors.

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Table 2. Univariate and Multivariate Analyses of Variables for OS in Patients with Recurrence (n = 234).

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

4. 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]. In addition, 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 radical resection to recurrence in other carcinomas [6-10] and HNSCC [12,21]. In all reports, patients with ER had a significantly worse prognosis than those with LR. In addition, few studies have demonstrated 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, similar to the present study [11,20,24]. Among them, 2 previous studies defined cases with a recurrence-free interval of less than 12 months as ER, whereas the remaining, which were similar to ours, defined recurrence in less than 6 months as ER. All of them concluded that a longer recurrence-free interval leads to a better prognosis. In the present study, we defined ER as recurrence within six months. This is due to 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 resistant to only platinum or originally resistant to any treatment modality. The

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results of the present study suggest that the prognosis is poor for patients with ER regardless of the treatment modality; thus, the poor prognosis of platinum-resistant patients may not have been due to platinum sensitivity only. The above shows that there are doubts on whether the concept of platinum resistance/sensitivity in the head and neck area captures the true nature of tumors.

ER 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 patients with ER has not been demonstrated. Some genomic and proteomic analyses have reported the possibility of identifying poor prognoses, but they are still in the research phase [26]. For this reason, the identification and selection of patients with ER before treatment are still difficult. In addition, even if patients are identified, preventive measures are difficult. This study also demonstrated the difficulties in improving the OS of patients with a poor prognosis. In fact, among the patients undergoing surgery, 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, all positive patients had a poor prognosis. This shows that even if multimodal treatment involving surgery, radiotherapy, and chemotherapy is performed, it is difficult to completely eliminate the poor prognostic environment as a tumor factor. To overcome this difficulty, trials involving preoperative immunotherapy using immune checkpoint inhibitors (ICIs) and their use as maintenance therapy after chemoradiotherapy or surgery as new strategies to improve OS are currently underway, and results are anticipated. In addition, 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 [27] that are based on the recurrence area, initial treatment content, and combined positive score before ICI use [28]. However, we conclude that changing salvage therapy depending on the recurrence status could also be a good strategy. In fact, in small-cell lung cancer, patients are divided into patients with sensitive relapse, in whom initial chemotherapy works and the interval to recurrence is long, and patients with refractory relapse, in whom the interval to recurrence is short and the treatment strategies are different [29,30]. Taking 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 selection risks of 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, 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 because of limitations in the sample size. To include all prognostic predictors in future studies, it is necessary to increase the sample size. This will help in obtaining more accurate estimates of recurrence risk.

5. Conclusions

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, and this study demonstrated the prognostic values of patients with ER. ER cases should be considered for different treatment strategies (e.g., addition of drugs) rather than LR cases because of the presumed poor prognostic factors of tumor characteristics.

Author 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.

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Informed Consent Statement: 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.

Data Availability Statement: The datasets generated and/or analysed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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