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Abstract

Objective

The increase in treatment options resulted in successful treatment with multiple lines of chemotherapy for recurrent and metastatic (RM) head and neck cancer (HNC). The present study aimed to elucidate the beneficial effect of successive treatment for RM-HNC.

Methods

We included 78 patients with RM-HNC who received one or multiple lines of chemotherapy from January 2008 to December 2019. We divided the patients into three groups according to treatment period: January 2008 to November 2012 included those who underwent cancer chemotherapy only with cytotoxic agents (Tox group), December 2012 to March 2017 included those who received cytotoxic agents and cetuximab (Cet group), and March 2017 to December 2019 included those who received cytotoxic agents, cetuximab and immune checkpoint inhibitor nivolumab (Nivo group). Moreover, we compared the overall survival of the three groups.

Results

In total, 18, 33, and 27 patients were included in the Tox, Cet, and Nivo groups, respectively. The median overall survival were 8.5 months in the Tox group, 16 months in the Cet group, and 19 months in the Nivo group, and the difference in the result was significant.

Conclusions

Successive treatment with second and subsequent lines of chemotherapy in patients with RM-HNC improves

prognosis.

Keywords: Recurrent and Metastatic, Head and Neck cancer, Second-line, Successive, Chemotherapy

Introduction

Head and neck cancer (HNC) is the sixth leading cancer worldwide, and approximately 630,000 new cases are recorded annually [1]. Most patients present with locoregionally advanced disease upon the initial diagnosis, and more than 50% have recurrence within 3 years [2–4]. Platinum-based chemotherapy, including cisplatin and carboplatin, has been the first-line treatment for recurrent and metastatic (RM)-HNC for a long time; however, the outcomes of this treatment were far from satisfactory. In addition to treatment with cisplatin and infusional fluorouracil, cetuximab significantly improves the overall survival of patients with RM-HNC in a first-line setting [5], and this combination therapy called EXTREME regimen has been a standard treatment for patients with RM-HNC.

Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody, which has an antitumor effect in patients with RM-HNC who are refractory to platinum-based chemotherapy [6]. This study, which was referred to as the CHECKMATE141 trial, revealed that nivolumab improved the overall survival of patients with RM-HNC in a second-line setting.

In Japan, the use of cetuximab and nivolumab for RM-HNC was approved in 2012 and 2017, respectively, based on the results of previous studies, which resulted to the increase in chemotherapy options and success in treatment with multiple regimens of chemotherapy. However, these studies were designed to elucidate the efficacy of a single treatment compared to the conventional treatment in a first- or second-line setting. Thus, the impact of successive treatment with second and subsequent lines of chemotherapy on the outcome of patients with RM-HNC has not been evaluated sufficiently.

Materials and Methods

The protocol of the investigation has been approved by the Institutional Review Board of Tottori University Hospital (No.19A131). A total of 78 patients received one or multiple lines of chemotherapy for RM-HNC between January 2008 and December 2019. These patients were divided into three groups: Patients treated with cytotoxic agents only from January 2008 to November 2012 were included in the Tox group (treatment options, including platinum-based chemotherapy with 5-fluorouracil, docetaxel, and S-1), those treated with cytotoxic agents and cetuximab from December 2012 to March 2017 in the Cet group (paclitaxel and cetuximab in addition to the treatment in the Tox group), and those treated with cytotoxic agents, cetuximab, and nivolumab from April 2017 to December 2019 in the Nivo group (nivolumab in addition to the treatment of the Cet group). Chemotherapy was provided to the patients until the occurrence of unmanageable toxicity or stopped due to disease progression, patient's demand, or death. Moreover, the overall survival of the three groups from the initiation of first-line treatment was retrospectively analyzed. The detail of the chemotherapeutic regimens was also evaluated. The mean numbers of treatment regimens were compared between the three groups. The objective response rate (ORR) and time to progression (TTP) of the patients who received nivolumab were also evaluated. ORR was assessed based on the Response Evaluation Criteria in Solid Tumor version 1.1 via computed tomography scan. Radiological evaluation was initially performed from 8 to 12 weeks after the initiation of first-line treatment and was repetitively performed every 8–24 weeks.

Statistical analysis was performed using GraphPad Prism 6. The mean number of treatments was compared between each group with Tukey's multiple comparison test. The overall survival of each group from the initiation of first-line treatment was calculated using the Kaplan–Meier method, and the trends of median survival were statistically analyzed with log-rank for trend.

Results

A total of 78 patients underwent one or multiple lines of chemotherapy for recurrent or metastatic disease during this study period: Tox group, n = 18; Cet group, n = 33; and Nivo group, n = 27 (Figure 1). The baseline characteristics of the patients are shown in Table 1. The characteristics of the three groups did not significantly differ.

Table 2 shows the details of chemotherapeutic regimens in each group. Approximately 30% of patients received nivolumab as the first-line treatment, and these patients experienced early recurrence or metastasis within 6 months after the initiation of chemotherapy or concurrent chemoradiotherapy, including cisplatin. The other 41% of patients received nivolumab as the second-line therapy. Most patients received EXTREME regimen as the first-line treatment. The patients who received nivolumab as greater than the fourth-line therapy experienced failure in all treatments and were treated with the newly approved nivolumab as the last treatment. The efficacy of nivolumab was evaluated, and the ORR was 7.4% and TTP 6 months.

In the Tox group, most patients received platinum-based therapy as the first-line therapy. Only 38.9% of the patients received the second-line treatment, 27.8% received over the second-line treatment, and 11.1% received the third-line treatment. None of the patients received over the third-line treatment. In the Cet group,

most patients received EXTREME regimen as the first-line therapy, 45.5% of the patients received the second-line treatment, 12.1% received over the second-line treatment, 18.2% over the third-line, and 9.1% over the fourth-line, however, only 6.1% received the fifth-line treatment. In the Nivo group, 88.8% of the patients received the second-line treatment, 25.9% received over the second-line treatment, 25.9% over the third-line, and 18.5% over the fourth-line, and 18.5% received the fifth-line treatment. The mean numbers of treatment regimens were 1.61 in the Tox group, 2.15 in the Cet group, and 3.115 in the Nivo group (Figure 2). The mean number of treatment regimens significantly increased in the Nivo group compared to the Tox and Cet groups (Tox vs Nivo, Cet vs Nivo, Tukey's multiple comparison test, $p < 0.05$), which indicated that the addition of newly approved chemotherapeutic agents influenced the increase in the mean number of treatments. The median overall survival rates were 8.5 months in the Tox group, 16 months in the Cet group, and 19 months in the Nivo group (Figure 3). The trend of improved overall survival was significant (log-rank for trend test, $p = 0.0482$). The addition of newly approved chemotherapeutic agents did not only increase the mean number of treatments but also prolonged the median overall survival.

Discussion

Platinum-based chemotherapy is the common first-line treatment for inoperable RM-HNC; however, the results of this treatment are far from satisfactory. In the past decades, many clinical trials with new chemotherapeutic agents and the combination of conventional therapy have improved the prognosis of patients with RM-HNC. The EXTREME trial showed a significant increase in overall survival with the addition of cetuximab to conventional platinum-based chemotherapy in a first-line setting [5]. The addition

of cetuximab prolonged the overall survival to about 2.7 months compared to platinum-based chemotherapy only. The CHECKMATE141 trial showed the efficacy of nivolumab in patients with RM-HNC who are refractory to platinum-based chemotherapy, and a previous study has shown that such treatment improves overall survival by 2.4 months compared to conventional standard therapy [6]. These studies have focused on the efficacy of treatment in a first- or second-line setting; thus, the impact of successive treatment with second and subsequent lines of chemotherapy on the outcome of patients with RM-HNC has not been evaluated sufficiently. In this study, we evaluated the impact of successive treatments in patients with RM-HNC by grouping the number of treatment options. The median overall survival significantly improved with the increasing number of treatment options. The difference in the median overall survival between the Cet and Tox groups was 7.5 months, and these data reflected survival benefit with the addition of cetuximab to conventional therapy, as shown in the EXTREME trial. The Cet group received not only cetuximab but also paclitaxel in 2012 compared to the Tox group. The survival benefit was found to be a result of the addition of not only cetuximab but also paclitaxel.

The treatment efficacy of nivolumab on ORR and TTP were far from satisfactory. However, this study revealed that Nivo group had the survival benefit on median overall survival compared to Cet group for 3 months. In this study, the mean number of treatment regimens was significantly higher in the Nivo group than in the Cet and Tox groups. Moreover, chemotherapy after administering nivolumab treatment might demonstrate greater effectiveness than expected [7]. Thus, survival benefit might be associated with the increase in treatment options and successive treatments with second and subsequent lines of therapies.

However successive treatment may also be harmful for patients with RM-HNC due to its adverse effects. Inappropriate succession of chemotherapy may have harmful effects on activities of daily living, which leads to decreased quality of life and worse prognosis. Assessing performance status and performing blood examination and evaluation using CTCAE can be helpful in appropriately assessing the tolerance. Chemotherapy should be successful in patients with good performance status (PS of 0–1 and selected 2) and less than grade 3 adverse events.

The present retrospective study had some limitations. First, this study included some uncommon HNC patients with nasopharynx, salivary gland, and paranasal sinus; additionally, those with non-squamous cell carcinoma were also included. The background of the patients was different from the data of clinical trials. Second, the effects of supportive care were not evaluated in this study.

Conclusion

Successive treatment with second and subsequent lines of chemotherapy in patients with RM-HNC improves prognosis from the initiation of first-line therapy. If the PS of the patients was consistent, clinicians should consider providing second and subsequent lines of chemotherapy and using all treatment options subsequently. However, inappropriate succession of chemotherapy may be harmful in patients with RM-HNC as it leads to decreased quality of life and worse prognosis. Assessing PS and performing blood examination and evaluation using CTCAE can be helpful in appropriately assessing the tolerance.

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Disclosure statement

We have no conflict of interest in this study. We have no financial support to declare this study.

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Tables

Table 1 Clinical characteristics of the three groups

The background characteristics of the three groups did not significantly differ. SCC: squamous cell carcinoma. *: Kruskal–Wallis test †: Chi-square test.

Table 2 Details of the chemotherapeutic regimens

This table shows the details of the chemotherapeutic regimens. In the Tox group, 83.3% of patients received platinum-based therapy as the first-line therapy. In the Cet group, 69.7% of patients received EXTREME regimen as the first-line therapy, and paclitaxel alone was the most frequent regimen as the second-line therapy. Approximately 30% of the patients in the Nivo group were treated with nivolumab as the first-line therapy because they were refractory to platinum-based therapy as the definitive chemoradiotherapy within 6 months. Another 42% of the patients who were refractory to first-line treatment with platinum-based therapy received the second-line treatment.

Figure Legends

Figure 1 Schematic diagram of the study.

The patients were divided into three groups: The patients who were treated with cytotoxic agents only from January 2008 to November 2012 were included in the Tox group, those treated with cytotoxic agents and cetuximab from December 2012 to March 2017 in the Cet group, and those treated with cytotoxic agents, cetuximab, and nivolumab from April 2017 to December 2019 in the Nivo group. Approved

chemotherapeutic agents are listed below each periods.

Figure 2 Percentage of the number of treatment regimens received by the patients of the three groups.

Figure 3 Overall survival of the three groups.

The median overall survival rates were 8.5 months in the Tox group, 16 months in the Cet group, and 19 months in the Nivo group. The trend of improved overall survival was significant (log-rank for trend test, $p=0.0482$).

Fig. 1.

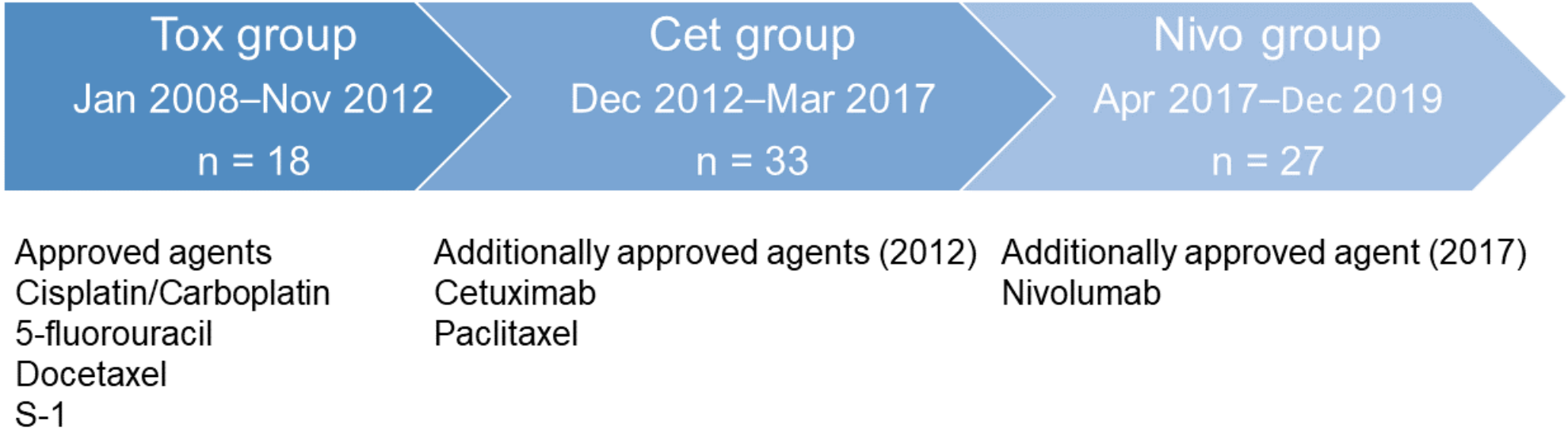
Tox group
Jan 2008–Nov 2012
n = 18
Cet group
Dec 2012–Mar 2017
n = 33
Nivo group
Apr 2017–Dec 2019
n = 27
Approved agents
Cisplatin/Carboplatin
5-fluorouracil
Docetaxel
S-1
Additionally approved agents (2012)
Cetuximab
Paclitaxel
Additionally approved agent (2017)
Nivolumab

Fig. 2.

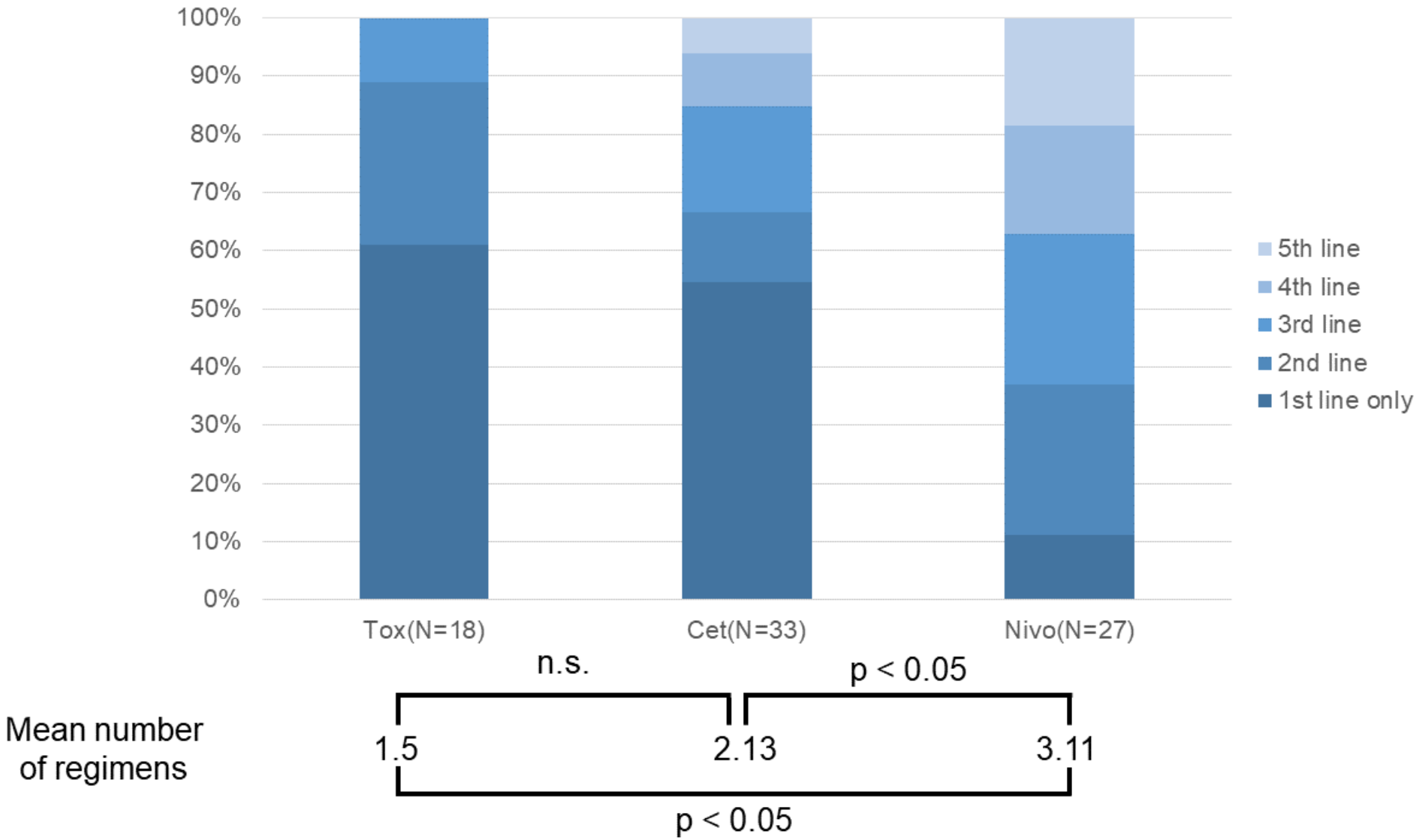
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Tox(N=18)
Cet(N=33)
Nivo(N=27)
5th line
4th line
3rd line
2nd line
1st line only
n.s.
p < 0.05
Mean number of regimens
1.5
2.13
3.11
p < 0.05

Fig. 3.

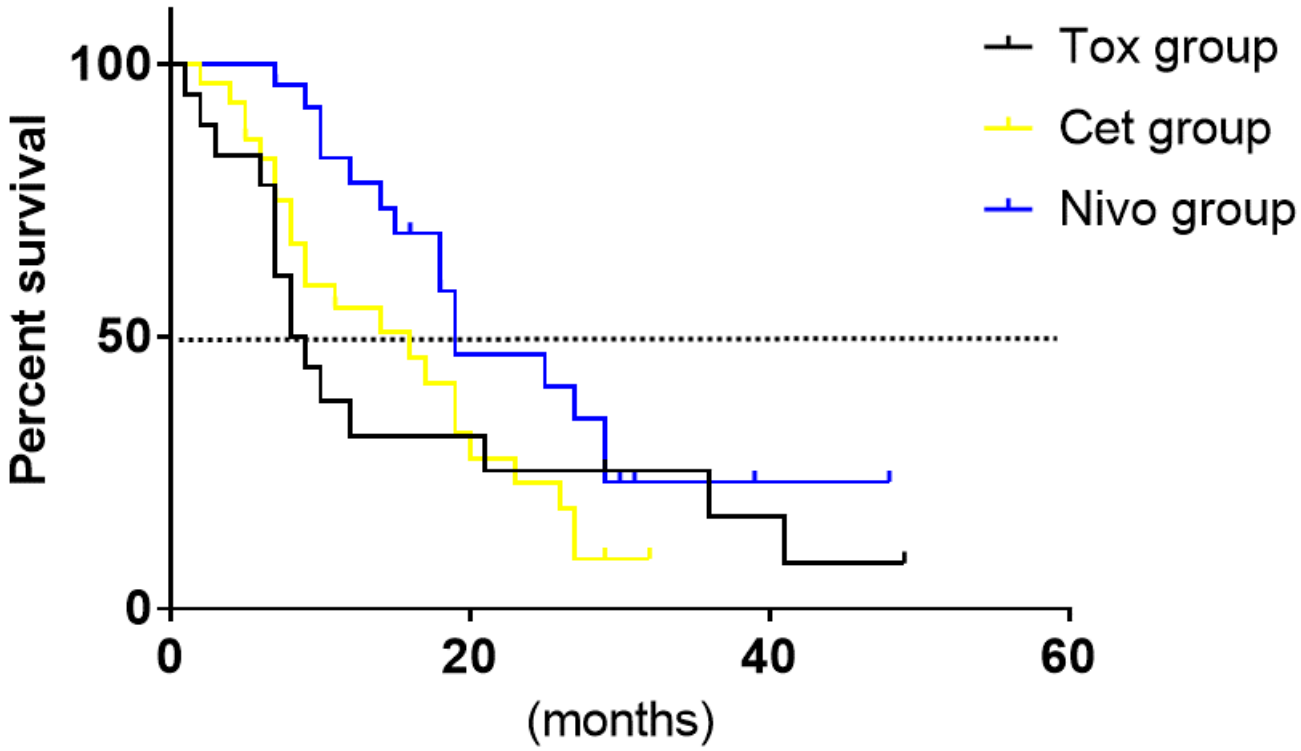
Percent survival
100
50
0
0
20
40
60
(months)
Tox group
Cet group
Nivo group

table 1

		Tox group (n = 18)	Cet group (n = 33)	Nivo group (n = 27)	p value
Age		66 (52–86)	67 (42–87)	68(40–79)	0.9666*
Sex		17:1	27:6	23:4	0.0875†
Smoke (Brinkman index)		622(0–1400)	652(0–3200)	634(0–1750)	0.6349*
Performance status	0	15	24	24	0.273†
	1–2	3	9	3	
Primary site	Hypopharynx	6	11	7	0.5622†
	Oropharynx	2	7	5	
	Larynx	4	5	1	
	Oral cavity	2	2	5	
	Others	4	8	9	
Stage	I and II	1	5	1	0.6148†
	III	1	3	2	
	IV	13	25	24	
Histology	SCC	16	29	22	0.7871†
	non-SCC	3	4	5	
HPV status	Positive	0	0	1	0.3842†
	Negative or Not evaluated	18	33	26	
Previous Treatment	Surgery	12	20	10	0.919†
	Radiotherapy	12	19	11	
	Chemotherapy	10	22	14	

table 2

	Tox（N=18)					Cet (N=33)					Nivo (N=27)				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Platinum-based	15	1	2	0	0	7	0	0	0	0	2	0	1	0	0
C-mab+Platinum	0	0	0	0	0	23	6	2	0	1	15	1	1	0	0
Nivo	0	0	0	0	0	0	0	0	0	0	8	11	2	4	2
C-mab+PTX	0	0	0	0	0	1	0	0	0	0	1	6	0	0	0
PTX	0	0	0	0	0	0	7	3	3	0	0	6	10	0	0
S-1	1	4	0	0	0	1	1	5	1	1	1	0	3	3	0
DTX	1	0	0	0	0	0	0	1	1	0	0	0	0	3	3
Other	1	2	0	0	0	1	1	0	0	0	0	0	0	0	0
Total	18	7	2	0	0	33	15	11	5	2	27	24	17	10	5