Original Article

Long-Term Observation of Advanced Nasopharyngeal Squamous Cell Carcinomas Treated Using a Combination Strategy

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Objectives: To improve the survival rate in patients with nasopharyngeal squamous cell carcinoma (NSCC).

Material and Methods: A total of 56 patients with NSCC were enrolled in this study, in order to observe the long-term survival. The primary site was treated conservatively with neoadjuvant chemotherapy (NAC) and concurrent chemoradiation therapy (CCRT), using superselective intra-arterial infusion chemotherapy (SSIAC) with cisplatin, docetaxel, and 5-fluorouracil. Cervical lymph node metastasis was treated using neck dissection.

Results: The 5- and 10-year overall survival rates were 67.9 and 60.5%, respectively. The 5- and 10-year survival rates improved particularly in patients with T3 cancer (96.5 and 96.5%, respectively), N1 cancer (100 and 100%, respectively), and poorly-differentiated cancer (88.2 and 79.2%, respectively). In contrast, the 5- and 10-year survival rates were worse in patients with T4 cancer (28.7 and 0%, respectively), N3 cancer (11.1 and 0%, respectively), and moderately-differentiated cancer (18.7 and 0%, respectively). There were significant differences in the overall survival rates between patients with stage III and IVA, stage III and IVB, and between IVA and IVB NSCC.

Conclusion: We demonstrated that NAC and CCRT using SSIAC, with neck dissection to control cervical lymph node metastasis, were safe and effective in patients with NSCC. The introduction of maintenance therapy and intensity-modulated radiation therapy (IMRT), as well as molecular-targeted drugs and heavy-particle radiotherapy, should be considered.

Key words: superselective intra-arterial infusion chemotherapy, squamous cell carcinoma, neoadjuvant chemotherapy, concurrent chemoradiation therapy, neck dissection

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Introduction

Surgery is not ordinarily first choice for advanced nasopharyngeal cancer (NPC) because of its location behind the nasal cavity and beneath the skull base. Histologically, NPC originates from ciliated epithelial cells, and Epstein-Barr virus infection and eating habits have been suggested as possible etiological factors¹⁾.

The prevalence of NPC differs among ethnic groups and regions, and is more common among Chinese in Southeast Asia and Hong Kong. There is no clear prevalence peak in young adults in the commonly-affected regions such as Southeast Asia, in contrast to regions such as Japan, where it is less common¹⁾. NPC is relatively sensitive to radiation therapy and chemotherapy, possibly because of viral involvement, but tends to be associated with early cervical lymph node metastasis, as well as repeated recurrence and metastasis at the primary site and cervical lymph nodes. However, to the best of our knowledge, no

accurate prognostic data based on TN classification are available.

The pathological classification of NPC was revised from the previous World Health Organization classification into the following three categories in 2005: keratinizing squamous cell carcinoma (SCC), nonkeratinizing carcinoma, and basaloid SCC²⁾. The histopathological prevalences of these subtypes differ. Keratinizing squamous cell carcinoma accounts for approximately 25% of NPCs according to the intergroup study 0099 (IGS0099) conducted mainly in North America³⁾, and for approximately 20% of NPCs in Japan^{4,5)}. However, malignant immature tumors in the nasopharynx are hard to diagnose by histopathology, and their diagnosis depends exclusively on oncopathologists.

We have successfully treated SCC, which accounts for the majority of head and neck cancers (HNCs), by neoadjuvant chemotherapy (NAC) and concurrent chemoradiation therapy (CCRT) using superselective

intra-arterial infusion chemotherapy (SSIAC) to control the primary site, with neck dissection to control cervical lymph node metastasis. This treatment has yielded high overall survival and functional organ-preservation rates in patients with tongue cancer, oropharyngeal cancer, hypopharyngeal cancer, and laryngeal cancer⁶⁻⁹.

Surgery is not ordinarily first choice for advanced NPC at the primary site. However, in this study we report the outcomes of NAC and CCRT using SSIAC to control the primary site, and neck dissection to control cervical lymph node metastasis in patients with NPC. We also consider if the primary site, cervical lymph node metastasis, or distant metastasis is the main prognostic factor in NPC, and discuss the optimal treatment in terms of survival.

Material and Methods

Patients

A total of 56 patients with nasopharyngeal SSC (NSSC) treated at Nihon University Hospital and related hospitals between April 2000 and May 2010 were included in the study. There were 45 male and 11 female, aged 37–72 years (mean: 62 years; median: 62 years). None of the patients had previously been treated for the disease. All patients were diagnosed with SCC according to the WHO classification (2005), which was well differentiated in 0 patients, well-to-moderately differentiated in 0 patients, moderately differentiated in 12 patients, moderate-to-poorly differentiated in 13 patients, and poorly differentiated in 31 patients (Table 1).

Tumors were classified according to the seventh edition of the UICC classification (2009). T classification was T2 in two patients, T3 in 32 patients, and T4 in 22 patients. N classification was N0 in 0 patients, N1 in 26 patients, N2 in 21 patients, and N3 in nine patients. Staging was stage III in 34 patients, stage IVA in 13 patients, and stage IVB in nine patients (Table 2).

All 56 patients in this study had advanced cancer, diagnosed as SCC by an oncopathologist. All patients attended our hospital to receive treatment. Patients with T1 or N0 cancer were excluded from the study. The study only included patients who agreed to the principle that residual tumor at the primary site would be additionally nasopharyngectomies, and residual cervical lymph node metastasis would be treated by neck dissection. No patients were examined for Epstein-Barr virus infection.

Table 1 Patient demographics

n = 56	
Sex	
male	45
female	11
Age (years)	
mean	62 (37–72)
median	62
Subject characteristics	
untreated	56
previously-treated	0
recurrent	0
Histological type	
squamous cell carcinoma	56
well differentiated	0
well-moderately differentiated	0
moderately differentiated	12
moderate-poorly differentiated	13
poorly differentiated	31

Table 2 TNM classification of patients (UICC 7th edition 2009) (n = 56)

	N0	N1	N2	N3
T1				
T2			2	
T3		26	6	
T4			13	9

Table 3 Schedule of superselective intra-arterial infusion chemotherapy

	Day 1	Days 2–6
pre-hydration 2000 ml d.i.v.	hydration 3000 ml d.i.v.	hydration 2000 ml d.i.v.
	Docetaxel hydrate 50–60 mg/m ² i.a.	5-FU 600–750 mg/m ² /day d.i.v.
	CDDP 50–60 mg/m ² i.a.	
	Hydrocortisone 300 mg/body i.a.	
	STS 9 g/m ² i.v.	
	STS 12 g/m ² d.i.v	

STS: sodium thiosulfate

Methods

The femoral artery was catheterized under fluoroscopic guidance, and an artery feeding the tumor was identified for intra-arterial administration of docetaxel (DOC) (60 mg/m^2) and cisplatin (CDDP) (60 mg/m^2) over 30–60 min. The neutralizing agent sodium thiosulfate was administered intravenously immediately before administration of CDDP. After administration of the anticancer drugs, hydrocortisone was administered intra-arterially to protect vascular endothelial cells and prevent vomiting. Starting on day 2, 5-fluorouracil (5-FU) ($750 \text{ mg/m}^2/\text{day}$) was administered by continuous intravenous infusion over 120 h. During CCRT, the doses of DOC, CDDP, and 5-FU were reduced to 50 mg/m^2 , 50 mg/m^2 , and $600 \text{ mg/m}^2/\text{day}$, respectively (Table 3).

Two courses of SSIAC were administered as NAC, followed by CCRT containing additional courses of SSIAC. A total of four courses of SSIAC were administered (Fig. 1).

Radiation therapy (RT) was administered at 66 Gy, but the radiation field was gradually reduced so that the dose in the spinal cord did not exceed 40 Gy. All patients received conventional three-dimensional conformal radiation therapy (3DCRT), and none received intensity-modulated radiation therapy (IMRT). Residual tumor at the primary site was additionally nasopharyngectomies, and cervical lymph node metastasis unresponsive to radiotherapy was treated aggressively by neck dissection (Fig. 1).

Analysis

The antitumor efficacy (i.e. response) of the treatment was assessed according to the World Health Organization criteria (two-dimensional). After secondary lesions such as mucositis had resolved, a biopsy was performed for histological assessment in all patients, except those who had gross residual tumor

at the completion of radiation therapy.

Overall survival was analyzed using the Kaplan-Meier method. Differences between groups were analyzed using the log-rank test and generalized Wilcoxon's test, and population bias was examined using Student's *t*-test, Fisher's exact test, and the χ^2 test. Side effects were summarized using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (JCOG/ISCO version).

Results

Response to treatment at the primary site after NAC and CCRT

Of the 56 patients, 46, 10, 0, and 0 showed complete response (CR), partial response (PR), no change (NC), and progressive disease (PD) at the primary site, respectively, with an overall response rate of 100% and a CR rate of 82.1%. The nasopharyngectomies were carried out in 10 cases with via maxillary swing approach in 7 cases, transcervical approach in 2 cases and transpalatal approach in one case.

Neck dissection after NAC and CCRT

Of the 56 patients, 30 patients (53.6%) underwent neck dissection, including one (3.8%) of 26 patients with N1 cancer, 20 (95.2%) of 21 patients with N2 cancer, and nine (100%) of nine patients with N3 cancer. Neck dissection was therefore performed more frequently in patients with N2 and N3 tumors.

Overall survival

The 5- and 10-year overall survival rates in the 56 patients were 67.9 and 60.5%, respectively (follow-up: 471–4493 days; median: 1918.5 days) (Fig. 2).

Overall survival and stage classification (Kaplan-Meier method)

The 5- and 10-year overall survival rates in the 34

Fig. 1
Treatment strategy.

Fig. 2 Overall survival rate and stage classification (Kaplan-Meier method).

Statistically significant differences were observed in the overall survival rates ($P < 0.001$) between stage III and IVA, between stage III and IVB, and between stage IVA and IVB.

Fig. 3 Overall survival rate and T classification (Kaplan-Meier method).

There was no significant difference in overall survival between patients with T2 cancer and those with T3 cancer ($P = 0.43$), or between patients with T2 cancer and those with T4 cancer ($P = 0.17$). The overall survival rate was significantly higher in patients with T3 cancer compared with those with T4 cancer ($P < 0.001$).

stage III patients were 96.7 and 96.7%, respectively (follow-up: 841–4493 days; median: 2571.5 days). The equivalent survival rates in the 13 stage IVA patients were 41.9 and 0% (follow-up 882–2641 days; median, 1455 days), and in the nine stage IVB patients were 11.1 and 0%, respectively (follow-up 471–1947 days; median, 1406 days).

Statistically significant differences were observed in the overall survival rates ($P < 0.001$) between stage III and IVA, between stage III and IVB, and between stage IVA and IVB (Fig. 2).

Overall survival and T classifications (Kaplan-Meier method)

The 5- and 10-year overall survival rates in the two patients with T2 cancer were both 100% (follow-up: 2566–4317 days; median: 3441.5 days). The

equivalent survival rates in the 32 patients with T3 cancer were 96.5 and 96.5% (follow-up: 841–4493 days; median: 2561.5 days), and in the 22 patients with T4 cancer were 28.7 and 0%, respectively (follow-up: 471–2641 days; median: 1430.5 days). There were no significant differences in overall survival between patients with T2 cancer and those with T3 cancer ($P = 0.43$), or between patients with T2 cancer and those with T4 cancer ($P = 0.17$). However, overall survival was significantly higher in patients with T3 cancer compared with T4 cancer ($P < 0.001$) (Fig. 3). In brief, overall survival was very low in patients with T4 cancer (Fig. 3).

Overall survival and N classification (Kaplan-Meier method)

The 5- and 10-year overall survival rates in the 26

Fig. 4 Overall survival rate and N classification (Kaplan-Meier method).

There was no significant difference in overall survival between patients with N1 and N2 cancer ($P = 0.34$). However, overall survival rates were significantly higher in patients with N1 and N2 cancers compared with those with N3 cancer (both $P < 0.001$).

Fig. 5 Overall survival rate and pathological classification (Kaplan-Meier method).

Overall survival rates were significantly higher in patients with moderate-to-poorly-differentiated SCC compared with those with moderately-differentiated SCC ($P < 0.001$), and higher in patients with poorly-differentiated SCC compared with those moderately-differentiated SCC ($P < 0.001$). However, there was no significant difference in survival between patients with moderate-to-poorly differentiated SCC and those with poorly-differentiated SCC ($P = 0.47$).

patients with N1 cancer were both 100% (follow-up: 841–4493 days; median: 2431.5 days). The equivalent rates in the 21 patients with N2 cancer were 60.3 and 49.7% (follow-up: 882–4317 days; median: 1991 days), and in the nine patients with N3 cancer were 11.1 and 0%, respectively (follow-up: 471–1947 days; median: 1406 days) (Fig. 4). There was no significant difference in survival rates between patients with N1 cancer and those with N2 cancer ($P = 0.34$). However, overall survival rates were significantly higher in patients with N1 or N2 cancer compared with those with N3 cancer (both $P < 0.001$). In brief, overall survival rates were very low in patients with N3 cancer (Fig. 4).

Overall survival and pathological classification (Kaplan-Meier method)

The 5- and 10-year overall survival rates in the 12 patients with moderately-differentiated SCC were 18.7 and 0%, respectively (follow-up: 471–3187 days; median: 1311 days). The equivalent survival rates in the 13 patients with moderate-to-poorly-differentiated SCC were 68.3 and 0% (follow-up: 974–3683 days; median: 1981 days), and in the 31 patients with poorly-differentiated SCC were 88.3 and 79.2%, respectively (follow-up: 841–4493 days; median: 2343 days). In summary, overall survival was significantly higher in patients with moderate-to-poorly-differentiated SCC compared with those

with moderately-differentiated SCC ($P < 0.001$), and significantly higher in patients poorly-differentiated SCC compared with moderately-differentiated SCC ($P < 0.001$). However, there was no significant difference between patients with moderate-to-poorly-differentiated SCC and those with poorly-differentiated SCC ($P = 0.47$) (Fig. 5). In brief, the overall survival rates were very low in patients with moderately-differentiated SCC (Fig. 5).

Toxicities and complications

Alopecia related to DOC was observed in 55 patients (98.2%). Other side effects of grade 3 or more in severity included leukopenia in 16 patients (28.6%) and neutropenia in 16 patients (28.6%). Hypochromia, thrombocytopenia, and hepatic dysfunction were rarely observed. Mucositis (26 patients; 46.4%) and dermatitis (21 patients; 37.5%) of grade 3 or more were frequently observed, because all 56 patients received CCRT. All the observed side effects were reversible (Table 4). There were no puncture- or infusion-related complications, including thrombus formation, embolism, nerve paralysis, angiospasm, hemorrhage, or other sequelae.

Discussion

En bloc surgery involving total resection of the

primary site and cervical lymph node metastasis has traditionally been recommended for the treatment of HNC, but this is now changing because of advancements in CCRT. The main causes of death because of HNC are broadly classified as failure to control the primary site, failure to control cervical lymph node metastasis, and distant metastasis. Head and neck surgeons and oncologists can contribute to functional organ preservation and survival in many patients with HNC by improving their knowledge and skills. However, surgery is not recommended as a first choice in the advanced NPC (SCC) for anatomical reasons, and the primary site has to be controlled in a conservative manner. These differences between NPC and HNCs in other regions thus need to be considered.

EBV is thought to be involved in the etiology of NPC, in addition to well-known factors such as cigarettes and alcohol. NPC originates from ciliated epithelial cells and is clinically responsive to radiation therapy, but tends to be associated with recurrence at the primary site, regional lymph node metastasis, and distant metastasis.

We consider that the progression of NPC is more closely correlated with prognosis since revision of the WHO pathological classification in 2005, and alterations of T2 in the UICC TNM classification in 2009. However, there is still a gap in the N classification, especially N2, compared with other HNCs.

In this study, treatment was initiated with two courses of NAC consisting of DOC and CDDP, given using SSIAC, together with 5-FU given by continuous intravenous infusion. NAC was followed by CCRT containing two courses of SSIAC with DOC, CDDP, and continuous intravenous infusion with 5-FU, together with irradiation at 66 Gy (Table 3). Any residual cervical lymph node metastasis was treated by neck dissection. However, previous studies, including contrast studies, have shown that anticancer drugs are not well-distributed in cervical lymph node metastases, which would therefore not be expected to be substantially controlled by SSIAC. Cervical lymph

Table 4 Treatment toxicity (n = 56)

	CTCAE grade			
	G1	G2	G3	G4
Decreased hemoglobin	19	14	6	
Decreased leukocyte count	11	23	12	4
Decreased neutrophil count	11	23	11	5
Decreased platelet count	4	2		
Hepatic dysfunction	17	12	3	
Nausea	11	3		
Alopecia	5	50		
Mucositis	13	17	26	
Dermatitis	7	7	21	

Table 5 Outcomes of treatment in patients with nasopharyngeal cancer

Author	Year	Drug	No. of pts	Stage	Overall survival (chemo-RT vs. RT)	P value
Neoadjuvant chemo						
Ma et al. ¹⁰⁾	2001	CDDP, 5-FU, BLM	456	III, IV	5 years (63 vs. 56%)	NS
Rossi et al. ¹⁷⁾	1988	VCR, CPA, ADM	229	I-IV	4 years (59 vs. 67%)	NS
Chi et al. ¹⁸⁾	2002	CDDP, 5-FU, LV	157	IV	5 years (61 vs. 55%)	NS
Concurrent chemo-RT						
Lin et al. ¹¹⁾	2003	CDDP, 5-FU	284	III, IV	5 years (72 vs. 54%)	0.0022
Concurrent chemo-RT + adjuvant chemo						
Al-Sarraf et al. ³⁾	1998	CDDP, 5-FU	193	III, IV	3 years (78 vs. 47%)	0.005

CDDP: cisplatin, 5-FU: 5-fluorouracil, BLM: bleomycin, VCR: vincristine, CPA: cyclophosphamide, ADM: adriamycin, LV: leucovorin.

node metastasis was therefore treated aggressively by neck dissection. This treatment was associated with relatively good outcomes, with 5- and 10-year overall survival rates of 67.9 and 60.5% in the 56 patients (stage III + IV), respectively.

We compared our results with treatment outcomes reported in previous studies to assess the characteristics of curable NPC. As shown in Table 5, the treatment outcome of NPC is generally better in patients treated with radiation therapy combined with chemotherapy, compared with radiation therapy alone, in terms of overall survival.

Chemotherapy can be broadly classified into NAC, CCRT, and CCRT plus adjuvant chemotherapy, according to the timing of administration (Table 5). A study of NAC with CDDP, 5-FU, and bleomycin showed that the 5-year overall survival rates in 456 stage III or IV patients were 63% with chemoradiation therapy, and 56% with radiation therapy alone¹⁰. Treatment of 284 stage III or IV patients with CCRT with CDDP and 5-FU found 5-year overall survival rates of 72% with chemoradiation therapy, and 54% with radiation therapy alone ($P = 0.0022$)¹¹. A study of CCRT plus adjuvant chemotherapy with CDDP and 5-FU demonstrated a 3-year overall survival rate of 78% in 193 stage III or IV patients treated with chemoradiation therapy, compared with only 47% with radiation therapy alone ($P = 0.005$)³.

In contrast, undifferentiated carcinoma and anaplastic carcinoma are generally considered to be more sensitive to radiation therapy than keratinizing SCC, which may produce a bias when comparing treatment outcomes between Southeast Asia and Western countries¹².

NPC is difficult to diagnose pathologically. In the present study, we therefore only included patients with previously-untreated NPC with no distant metastasis, which was diagnosed by an oncopathologist as NSCC. Patients diagnosed with undifferentiated carcinoma or anaplastic carcinoma were excluded.

Because of advanced NPC is located in anatomically difficultly operable region, we attempted to control the primary site by NAC and CCRT using SSIAC, and treat residual cervical lymph node metastasis by neck dissection. This treatment resulted in satisfactory outcomes, with 5- and 10-year overall survival rates of 67.9 and 60.5%, respectively. A better outcome may have been achieved if patients with so-called undifferentiated or anaplastic carcinoma had been included in the study. Previous studies have examined the use of CDDP, DOC, and 5-FU^{13,14} in SCC, and we also had data from histoculture drug-response assays demonstrating efficacy of CDDP, DOC, and 5-FU for SCC. However, we had little data regarding histoculture drug-response assays for undifferentiated

or anaplastic carcinoma, and we therefore excluded these patients from the study for their own benefit.

According to T classification, the 5- and 10-year overall survival rates were both significantly higher in patients with T3 disease compared with T4 disease. Similarly the 5- and 10-year overall survival rates were significantly higher in patients with N1, compared with N3 cancer, while the survival rate was approximately 50% in patients with N2 cancer.

Thus although stage III and IV disease were integrated into advanced cancer in the above mentioned studies (Table 5), we observed significant differences in overall survival rates among patients with stage III, IVA, and IVB disease in the current study ($P < 0.001$).

In summary, a 10-year overall survival rate of 100% may be expected in patients with stage T3N1M0 or earlier. However, in contrast, even 5-year survival cannot be expected in T4N3 disease. In N2 disease involving bilateral cervical lymph node metastasis, the overall survival rate was approximately 50%, probably because cervical lymph node metastasis on either side had to be treated by modified neck dissection to prevent damage incurred by bilateral ligation of the internal jugular veins during bilateral neck dissection. This treatment resulted in CR in several patients with T4 or N2-3 cancer. Indeed, 53.8% of T4N2M0 patients and 55.6% of T4N3M0 patients became cancer-free at least at once, indicating that the common causes of death because of NPC were recurrence and metastasis. Given that cervical lymph metastasis can be controlled by neck dissection to some extent, this suggests that control of the primary site may be the most important prognostic factor for NPC.

Because NSCC, a new class of NPC, is highly sensitive to treatment with CDDP, DOC, and 5-FU, only patients with a histological diagnosis of SCC were included in the present study. Comparison of the 5- and 10-year overall survival rates according to the degree of differentiation showed good outcomes in patients with poorly-differentiated tumors (88.3 and 79.2%, respectively), lower rates in those with moderate-to-poorly-differentiated SCC (68.3 and 0%, respectively), and poor outcomes in patients with moderately-differentiated SCC (18.7 and 0%, respectively), indicating that the outcome was generally very good in patients with poorly-differentiated SCC, but very poor in those with moderately-differentiated SCC in terms of overall survival. This suggests that the current treatment strategy was more effective for immature cells.

The standard therapy for NPC in the US is CCRT and adjuvant therapy³. We previously reported the usefulness of maintenance therapy for HNC¹⁵, and maintenance therapy may thus also improve the outcome of NPC.

The current treatment protocol resulted in good outcomes, but the total doses of CDDP, DOC, and 5-FU reached 220, 220, and 13,500 mg/m², respectively. Given the possibility of multi-drug resistance¹⁶⁾, the introduction of other drugs with different mechanisms of action, such as molecular-targeted drugs, should be considered.

Conclusions

NAC and CCRT using SSIAC, with neck dissection to control cervical lymph node metastasis, offers a safe and effective option for patients with NSSC. However additional therapy for patients with residual tumor, and maintenance therapy for patients with CR may be required such as nasopharyngectomies. To avoid multi-drug resistance, drugs with different mechanisms of action, such as molecular-targeted drugs, might be introduced, and IMRT and heavy-particle radiotherapy might also be considered. Further modifications of this treatment strategy may be expected to improve the treatment outcomes in patients with NPC further.

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