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Role of induction chemotherapy for N3 head and neck squamous cell carcinoma

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ABSTRACT

Objective: The treatment of head and neck squamous cell carcinoma (HNSCC) with N3 (>6 cm) lymph nodes remains difficult, and the best treatment strategy has not been elucidated. The aim of this study was to evaluate the outcomes of various treatment modalities.
Methods: Sixty-nine patients with HNSCC and N3 neck disease treated with definitive therapy in our institute between 1987 and 2013 were included in the analysis. We compared the clinical outcomes of radiotherapy (RT) alone, chemoradiotherapy (CRT) and surgery with or without induction chemotherapy (ICT).
Results: The overall survival (OS) at three years for the patients with N3 neck disease was 41%. The three-year OS rates of patients treated with definitive surgery and definitive CRT were 41% and 48%, respectively. There were no significant differences between these two treatments ($P = 0.82$). The OS of patients who received ICT followed by definitive therapy was significantly better than that of patients who did not ($P < 0.001$). The most common recurrence pattern was distant metastases. The rate of distant metastases was 61% of all treatment failures (20/33).
Conclusion: The high rate of distant metastases in patients with N3 neck disease suggests that prevention of distant metastases can improve survival. Based on this study, we consider that ICT may play an important role in the treatment of N3 neck disease.

1. Introduction

Controlling cervical lymph node metastases is a major factor influencing the outcomes of treatment of head and neck squamous cell carcinoma (HNSCC) [1]. In particular, metastatic lymph nodes measuring >6 cm (N3) are classified as stage IVB lesions according to the American Joint Committee on Cancer (AJCC) Staging Manual edition 7 and have poorer treatment outcomes than N1/2 nodal metastases. A variety of approaches have been adopted in the treatment of N3 nodal disease, including induction chemotherapy (ICT), chemoradiotherapy (CRT) and surgery. The majority of cases of advanced neck disease are treated with a combination of chemotherapy, radiation and surgery. The use of combined modality therapy allows for the treatment of patients once considered inoperable and incurable.

However, the optimal treatment strategy for N3 neck disease remains a controversial issue. Although some authors have reported that the treatment outcomes of CRT for N3 disease are worse than those for surgery [2], CRT is often selected as the definitive treatment in patients with small T and bulky N disease. The role of neck dissection following CRT is also not evident. In addition, skin invasion cases are described as unresectable in the National Comprehensive Cancer Network (NCCN) guidelines. However, in our practice, some patients with skin invasion due to N3 neck disease treated with definitive surgery have obtained long-term survival without recurrence.

Although cisplatin-based ICT can reduce the incidence of metastasis [3,4], whether the addition of ICT to CRT improves the treatment efficacy compared with CRT alone is unclear. Few studies have included significant number of patients with N3 neck

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disease due to the relative scarcity of such a advanced disease [5–7]. The purpose of the present study was therefore to evaluate the outcomes of management of patients with N3 neck disease.

2. Materials and methods

2.1. Study population

From January 1987 to March 2013, a total of 81 patients with head and neck cancer and N3 neck disease were treated at the Aichi Cancer Center Central Hospital, Nagoya, Japan.

2.2. Collected information

Medical records were reviewed to obtain demographic information and data such as the primary tumor site, TNM stage, lymph node size, primary treatment, adjuvant treatment, treatment response based on clinical examinations and radiographic findings, site of recurrence, time to recurrence and death. cN3 neck disease was defined by the American Joint Committee on Cancer Staging Manual, edition 7, as any cervical lymph node measuring greater than 6 cm. Patients with primary nasopharynx, salivary gland or thyroid tumors and/or distant metastatic disease at the time of presentation were excluded. Patients treated with palliative therapy alone were also excluded.

The response to treatment was assessed using imaging (CT and/or MRI) and clinical examinations.

2.3. Treatment modalities

We divided the patients into three groups according to the definitive treatment: radiotherapy (RT) alone, chemoradiotherapy (CRT) or surgery. Induction chemotherapy (ICT) was defined as initial chemotherapy followed by definitive treatment. The treatment modalities were various because this study was an accumulation of cases over a long period. The basic criteria to select ICT and definitive treatment are shown below. In principle, ICT was provided for patients with any primary site. However, a certain number of patients who did not receive ICT in any primary site existed because ICT was not performed for some of the patients due to their refusal, or other reasons. For primary site, when patients with laryngeal and pharyngeal cancer showed more than 50% response after ICT, they were applied to CRT or RT treatment. Those who were nonresponders ($\leq$50% response) were applied to definitive surgery. Patients with other primary sites basically underwent surgery after ICT. For neck disease, we selected definitive treatments according to the response after ICT and the presence of carotid artery invasion for each patient.

2.3.1. Radiotherapy

For the patients treated with RT alone and CRT, definitive RT was administered with a conventional fraction (2 Gy/fraction once a day, five times a week). Treatment with 60–70 Gy was delivered as a curative dose to primary lesions and metastasis-positive lymph nodes. The treatment response was assessed using laryngoscopy, CT, MRI and/or PET/CT.

2.3.2. Induction chemotherapy

Most of the ICT regimens included FP. The FP regimen consisted of 5-fluorouracil (5-FU) (800 mg/m^2/day) on days 1–5 and cisplatin (80 mg/m^2/day) on day 6 for one to two cycles every three to four weeks. The weekly FP regimen consisted of 5-FU (1000 mg/m^2/day) on days 1–2 and cisplatin (25 mg/m^2/day) on day 1 for one to five cycles every week.

The TPF regimen consisted of 5-FU (750 mg/m^2/day) on days 1–5, cisplatin (70 mg/m^2/day) on day 1 and docetaxel (70 mg/m^2/day) on day 1 for two cycles every three to four weeks.

2.3.3. Concurrent chemoradiotherapy

All concurrent chemotherapy regimens were platinum-based. In the cisplatin regimen, cisplatin was delivered on a weekly (25–30 mg/m^2/day for one to six cycles) or every three-week (80 mg/m^2/day for three cycles) schedule. Other concurrent chemotherapy regimens included a combination of CDDP and 5-FU (FP) or nedaplatin (CDGP) and 5-FU (FN). The FP regimen consisted of 5-FU (800 mg/m^2) on days 1–5 and CDDP (50 mg/m^2) on days 6–7, while the FN regimen consisted of 5-FU (800 mg/m^2) on days 1–5 and CDGP (130 mg/m^2) on day 6. The FP and FN regimens were administered in principal three times at four-week intervals. Following the completion of these treatments, the patients were followed up at least every month for the first year, every two months for the second year and less frequently thereafter. Imaging was performed every three to six months, then subsequently as clinically indicated.

2.4. Statistical methods

All tests to determine statistical significance were two-sided, and statistical significance was defined as a P value of <0.05. Survival curves were plotted based on the Kaplan–Meier method, and categorical variables were compared using the log-rank test. Overall survival (OS) was defined as the time from the first date of treatment to the date of death or last contact. Disease-free survival (DFS) was defined as the time from the first date of treatment to the date of recurrence. Differences within groups were compared using Cox regression models. For the univariate analysis, we selected factors known to impact oncologic outcomes or patient and treatment characteristics. A multivariate analysis was performed to adjust for confounding prognostic variables with P values <0.10 in the univariate analysis in order to determine the impact of the risk factors on the outcomes. All analyses were performed using the R version 1.6-3 software program (R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Patient and tumor characteristics.

	Median (range)	n	%
Age	60 (36–80)		
Sex			
Male		65	94
Female		4	6
Primary tumor site			
Oropharynx		36	52
Hypopharynx		20	29
Unknown		4	6
Oral cavity		6	9
Larynx		3	4
Lymph node size (cm)	7.0 (6.1–11.5)		
T-classification			
Tx		4	6
T1		7	10
T2		20	29
T3		19	28
T4		19	28
Tumor differentiation			
Well		16	23
Moderately		26	38
Poorly		8	9
Not specified or missing		21	30