



Title	Regional control after concomitant chemoradiotherapy without planned neck dissection in node-positive head and neck squamous cell carcinomas
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Title:

Regional control after concomitant chemoradiotherapy without planned neck dissection in node-positive head and neck squamous cell carcinomas.

Abstract

Objectives: Although three-weekly high-dose (100mg/m²) cisplatin (three cycles) chemoradiotherapy has been considered a standard regimen for patients with advanced head and neck squamous cell carcinomas (HNSCC), this protocol is associated with significant acute and late toxicities. Therefore, weekly cisplatin at a dose of 40mg/m² has been used at our institution since 2006. This retrospective study was aimed at assessing the oncologic efficacy of weekly cisplatin chemoradiotherapy for the control of nodal metastasis.

Methods: We analyzed 28 patients with node-positive HNSCC treated with weekly cisplatin and concurrent radiotherapy. Computed tomography was performed 4-8 weeks after the completion of chemoradiotherapy to evaluate nodal response. If residual neck disease was apparent or suspected, we performed early salvage neck dissection (ND). In cases with a complete response (CR), we took a “wait and see” approach. When no viable tumor cells were observed in the surgical specimens obtained by ND, nodal metastasis was defined as controlled by weekly cisplatin chemoradiotherapy alone.

Results: Nodal metastasis was evaluated as having a CR in 20 patients (71%). Eight patients (29%) underwent early salvage ND. Recurrent primary tumors were observed in the other four patients (14%). Salvage primary resection and associated ND were performed for these four patients. In 7 of 12 patients undergoing ND, no viable tumor cells were observed. In 23 of 28 patients, neck diseases were controlled by chemoradiotherapy alone (not including salvage by ND). In 27 of 28 patients, neck diseases were controlled by the overall treatment (including salvage by ND). The rate of nodal control by chemoradiotherapy alone and by the overall treatment was found to be 82.0% and 96.3%, respectively, using the Kaplan-Meier method. The three-year overall and disease free survival rates were 86.8% and 80.8%, respectively.

Conclusion: Concomitant weekly cisplatin at a dose of 40mg/m² chemoradiotherapy showed a good control rate of not only primary lesions but also neck diseases.

KEY WORDS: head and neck cancer, chemoradiotherapy, lymph node metastasis, cisplatin, nodal control

INTRODUCTION

Lymph node metastasis is one of the most important prognostic factors for patients with head and neck squamous cell carcinomas (HNSCC). Although three-weekly high-dose (100mg/m²) cisplatin (three cycles) and radiotherapy has been considered a standard regimen for patients with advanced HNSCC, this protocol is associated with significant acute and late toxicities [1-4]. Furthermore, the completion rate for this regimen is relatively poor [1-2]. Therefore, weekly cisplatin at a dose of 40mg/m² has been used at our institution since 2006. We reported that weekly cisplatin was easier to manage than three-weekly cisplatin, because patients could be monitored more regularly for toxicity, thereby allowing the schedule to be altered if required [5]. This retrospective study was aimed at assessing the oncologic efficacy of concomitant weekly cisplatin chemoradiotherapy without planned neck dissection (ND) for the control of neck disease.

MATERIAL AND METHODS

Patients. Between July 2006 and May 2011, 59 patients with biopsy-proven HNSCC were treated with concurrent weekly cisplatin chemoradiotherapy. Twenty-two patients with N0, seven patients who underwent neo-adjuvant chemotherapy (using cisplatin, 5-fluorouracil, and docetaxel), and two patients who underwent upfront ND before chemoradiotherapy were excluded. The remaining 28 patients were eligible for this study. The primary site was the oropharynx in 12 patients (43%), the hypopharynx in 13 patients (46%), and the larynx in 3 patients (11%). The characteristics of these 28 patients are shown in Table 1. (Table 1) Approval for this study was obtained from the institutional review board at Hokkaido University. Completion of the survey was considered as implied consent for participation.

Pre-treatment evaluation. Physical examination and pre-treatment computed tomography (CT) and/or magnetic resonance imaging were performed for all patients. Positron emission tomography (PET) was used where possible. Patients were also evaluated by a multidisciplinary team consisting of head and neck surgeons, radiation oncologists, and medical

oncologists, and tumors were classified according to the American Joint Committee on Cancer (AJCC) staging system (6th edition, 2002). T and N classifications are shown in Table 2. (Table 2)

Chemotherapy. Cisplatin was administered at a dose of 40mg/m² on weeks 1, 2, 3, 5, 6, and 7 of the radiotherapy. Patients received prophylactic hydration and 5HT₃ antagonists plus dexamethasone for anti-emetic prophylaxis. The intended total dose of cisplatin was 240mg/m². The cisplatin dose was modified on a case-by-case basis according to the level of adverse events. In addition, weekly cisplatin was altered to weekly carboplatin [area under the curve (AUC)=1.5] in some cases based on the toxicity. Toxicities were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0.

Radiotherapy. The irradiation plan was 40 Gy in 20 fractions of 2 Gy over four weeks for the primary site and all nodal areas, immediately followed by a boost of 30 Gy in 15 fractions to the primary cancer and metastatic nodal area over an additional three weeks (total dose, 70 Gy).

Post-treatment evaluation and follow-up. There was no intention to perform planned ND patients after the completion of chemoradiotherapy. CT scans were performed 4-8 weeks after the completion of chemoradiotherapy to evaluate nodal response. CT scan criteria of less than 15mm for maximum diameter without any focal abnormalities were reported previously and were applied for evaluation of radiographic complete response (CR) in current study [6,7]. If residual neck disease was apparent or suspected, we performed early salvage ND. In cases with a radiographic CR based on CT, PET was applied 10-12 weeks after the completion of chemoradiotherapy for reconfirmation. In cases with a CR based both on CT and PET, we took a “wait and see” approach. Patients were usually monitored monthly for the detection of recurrence in the first year, every couple of months in the second year, and every 6 or 12 months thereafter. CT scans were routinely performed once every three months in the first year, and every 6 or 12 months thereafter. If lymph node and/or primary recurrence were observed in the follow-up CT, we performed salvage surgery. When no viable tumor cells were observed in the surgical specimens obtained by ND, nodal

metastasis was defined as controlled by weekly cisplatin chemoradiotherapy alone. When salvage ND was performed, we intended to preserve the internal jugular vein, sternocleidomastoid muscle, and the spinal accessory nerve, where possible. The extent of neck dissection included level II, III, IV. **Statistics.** The Kaplan-Meier method was applied for survival and control rates using JMP 9.0.2 statistical software (SAS Institute, Cary, NC). Time of interest was the duration from the start of treatment to death or failure.

RESULTS

Chemoradiotherapy. In all patients, a full dose of 70 Gy was achieved. Weekly cisplatin was administered a median of five times (range 1-6, mean 4.5 times). The median total cisplatin dose was 200mg/m² (range 40-240, mean 180mg/m²). Table 3 showed toxicities of chemoradiotherapy. (Table 3) Three patients were switched from concurrent chemotherapy to weekly carboplatin (AUC=1.5) a median of three times (range 2-6, mean 3.7 times) because of renal dysfunction in two patients, and liver dysfunction in one patient.

Salvage surgery. Primary tumors in all patients and lymph node metastases in 20 patients (71%) were evaluated as radiographic CR from the initial evaluation using CT scans. PET was applied in 18 of these 20 patients, and radiographic CR was reconfirmed without abnormal accumulation. In remaining two patients, PET was not used because of patient's wishes.

In eight patients (29%), lymph node metastases were considered to persist according to the initial CT evaluation. These eight patients underwent early salvage ND. In 3 of the 8 patients undergoing early salvage ND, viable tumor cells were observed in the surgical specimens. In the other four patients (14%), recurrent primary tumors were observed at a median of 23 weeks after the completion of chemoradiotherapy (range 21.4-44, mean 27.9 weeks), and salvage primary resection and associated ND were performed at a median of 27.1 weeks after the completion of chemoradiotherapy (range 25.4-48, mean 31.9 weeks). In 2 of the 4 patients undergoing associated ND, viable cancer cells were observed in the surgical specimens. (Figure 1)

Complications of salvage surgery. As to acute complications of salvage surgery, localized wound infection and following sepsis were observed in 1 of all 12 patients undergoing ND (8.3%). The patient underwent primary resection, associated ND, and pharyngeal reconstruction using free flap transfer due to recurrent oropharyngeal cancer one year after the completion of chemoradiotherapy.

As to late complications of salvage surgery, neck pain was observed in 2 of all 12 patients undergoing ND (16.7%). These two patients who underwent early salvage ND needed continuous medication. Neither neural dysfunction nor dysphagia was observed after salvage surgery in our current study.

Patient Outcomes. The median follow-up period for surviving patients was 28 months (range 8-62, mean 30 months). Three patients died of diseases. In one patient who underwent primary salvage resection and ND at 25.4 weeks after chemoradiotherapy, nodal recurrence was revealed three months after ND. This patient died from neck disease seven months after surgery. Another two patients died from primary recurrence and lung metastasis without nodal recurrence at 12.4 and 21.9 months after chemoradiotherapy. One patient remains alive with lung metastasis, and the other 24 patients remain alive without disease.

Analysis of nodal control and survival rates. In 23 of all 28 patients, neck diseases were controlled by weekly cisplatin chemoradiotherapy alone (not including salvage by ND). In 27 of all 28 patients, neck diseases were controlled by the overall treatment (including salvage by ND). Using the Kaplan-Meier method, the rate of nodal control by chemoradiotherapy alone and by the overall treatment was found to be 82.0% and 96.3%, respectively. (Figure 2) The three-year overall and disease-free survival rates were 86.8% and 80.8%, respectively. (Figure 3)

DISCUSSION

For patients with HNSCC, lymph node metastasis remains an important prognostic factor. Since the 1970's, planned ND combined with radiotherapy had been considered the standard treatment for these patients

[8]. This trend of planned ND was widely used as no modalities for the evaluation of nodal response had yet been developed. Some authors using planned ND reported good nodal control rates and revealed frequent residual nodal metastases in surgical specimens [9-11]. Therefore they supported the use of planned ND following radiotherapy. However, as more effective chemoradiotherapy regimens were employed, planned ND was no longer considered to be justified for patients who achieved a radiographic CR, according to a recent review [12].

Since performing ND has some drawbacks, such as like neck stiffness and occasional dysphagia, the general trend has been against the performance of planned ND recently. Therefore, we routinely proceeded without any intention to use planned ND and practiced a “ wait and see ” approach for patients with a radiographic CR.

For patients with HNSCC and lymph node metastasis, the nodal control rate of chemoradiotherapy was reported at 64.5%- 92% with or without planned ND [10,13-16]. Nouraei et.al. reported 41 patients treated with neo-adjuvant chemotherapy (5FU and cisplatin), and chemoradiotherapy with concurrent cisplatin 100mg/m² on day 1 and 22. All 41 patients in their study underwent planned NDs, and five-year nodal control rate was 92% [10]. Robbins et.al. reported 52 patients who underwent intra-arterial platinum chemotherapy and radiotherapy, with planned NDs performed for 34 of 52 patients with bulky metastatic nodes. The nodal control rate for these 52 patients was 91% [15].

Grabenbauer et.al. reported 97 patients undergoing platin-based chemoradiotherapy (radiotherapy median dose 70 Gy) with CR of the primary disease. Planned NDs were performed for 56 of 97 patients. Remaining 41 patients did not receive ND and were observed with “ wait and see ” approach. The nodal control rates for the planned ND patients and “ wait and see “ patients were 80% and 85%, respectively. It was concluded that there was no clear evidence for the routine clinical use of planned ND [16].

Although there was no intention to perform planned ND in the current study, the nodal control rate was comparable to recent reports.

Therefore, we consider that the strategy not to perform planned neck dissection and the application of a “ wait and see “ approach to be acceptable in patients with a radiographic CR.

For the continued use of a “ wait and see” approach requires, it is important for nodal response to be evaluated after the completion of chemoradiotherapy. Using CT scans after the completion of chemoradiotherapy was reported to be convenient and helpful in terms of accuracy (negative predictive value: 88.5-94%) [6,7]. Some authors advocated the use of post-treatment fludeoxyglucose [F18]- PET in determining the presence or absence of residual neck disease [17-19]. However, the technical and timing issues regarding the use of this modality in the assessment of treatment response during the early post-treatment period remain controversial.

For the reasons mentioned above, we initially use CT scans for the evaluation of nodal response at 4-8 weeks after the completion of chemoradiotherapy initially. For the patients with a radiographic CR based on the CT scans, the addition of PET-CT is suggested at 10-12 weeks post-treatment. If abnormal uptake in the PET-CT is found, we suggest salvage surgery. If no abnormalities are found in the PET-CT, we continue to apply a “ wait and see ” approach.

Concomitant chemotherapy based on cisplatin and radiotherapy is in widespread use for patients with HNSCC. The standard regimen of concurrent chemotherapy was previously considered to be three-weekly high-dose (100mg/m²) cisplatin (three cycles) [1-3]. However, a high frequency of significant acute and late toxicities was observed in association with this treatment regimen [1-4]. Because of these toxicities, it was difficult to apply this regimen at our institution. Therefore, we have used weekly cisplatin regimen at a dose of 40mg/m² at our institution since 2006. In our previous study, it was revealed that the application of concomitant weekly cisplatin chemotherapy and radiotherapy was safety and feasible [5]. In the current study, the nodal control rate for patients treated weekly cisplatin chemoradiotherapy was high. Therefore, it is considered that this new regimen appears to be a suitable alternative to three-weekly high dose

cisplatin with concomitant radiotherapy from the view points of not only primary disease control but also neck disease control.

CONCLUSIONS

Concomitant weekly cisplatin at a dose of 40mg/m² chemoradiotherapy with adequate salvage ND showed a good control rate of not only primary lesion but also neck disease. In the current study, the rate of nodal control by chemoradiotherapy alone and by the overall treatment was found to be 82.0% and 96.3%, respectively. The strategy to avoid planned neck dissection and the application of a “ wait and see “ approach were considered acceptable in patients with a radiographic CR.

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FIGURE LEGENDS

Figure 1. Patient outcomes

Abbreviations: CRT, chemoradiotherapy; N+, node-positive; rN+, radiographic node-positive; rCR, radiographic complete response; pN+, pathological node-positive; pCR, pathological complete response; ND, neck dissection; NED, no evidence of disease; AWD, alive with disease

Figure 2. Kaplan Meier estimation of nodal control rates among 28 HNSCC patients with nodal metastasis. When viable tumor cells were observed in the surgical specimens obtained by neck dissection, the nodal control by

weekly cisplatin chemoradiotherapy alone was defined as failure. The nodal control of overall treatment means including salvage by neck dissection.

Abbreviation: CRT, chemoradiotherapy

Figure 3. Kaplan Meier estimation of overall and disease free survival rates among 28 HNSCC patients with nodal metastasis.

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Figure 1.

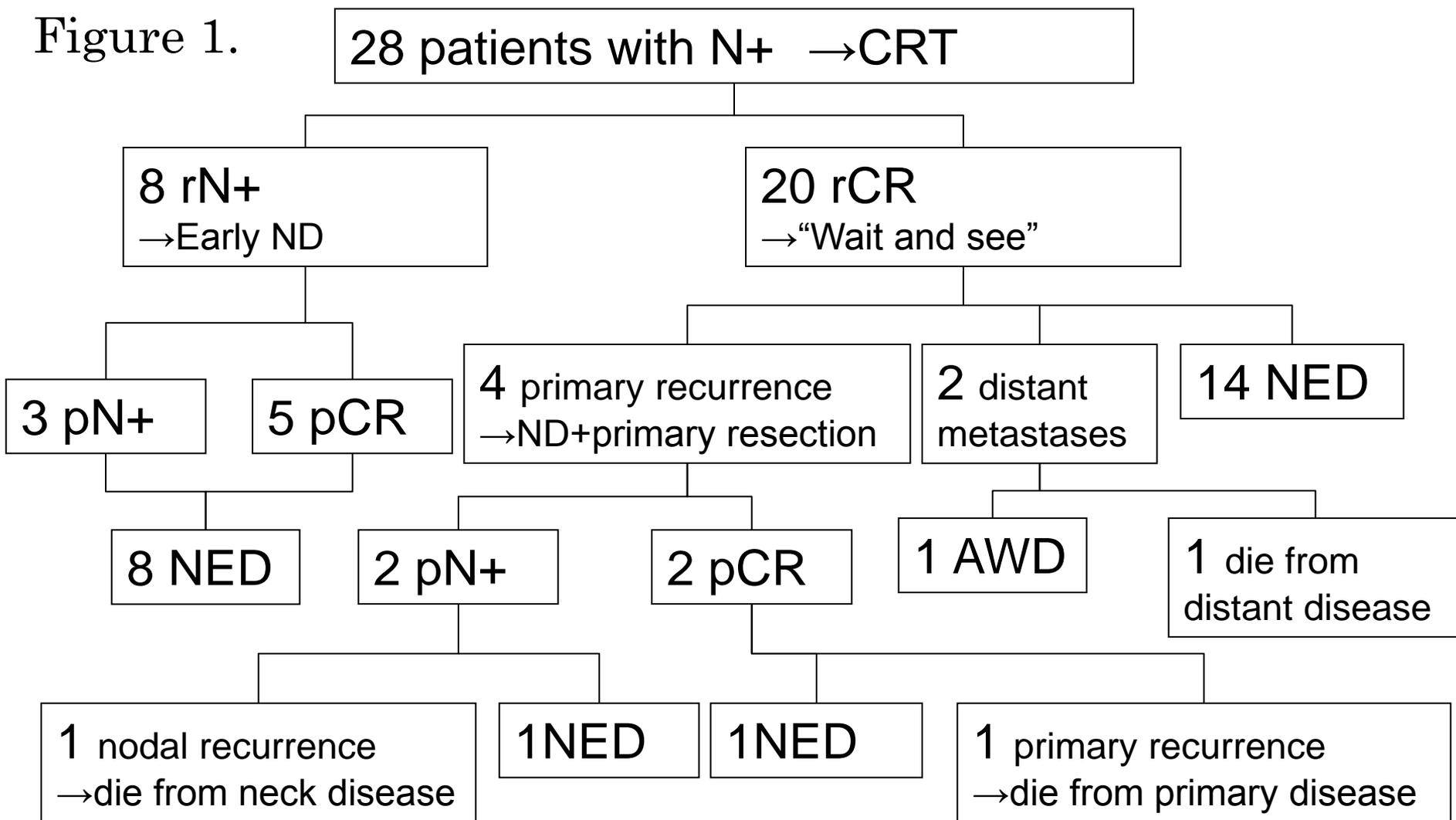


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Figure 2.

Nodal Control Rates

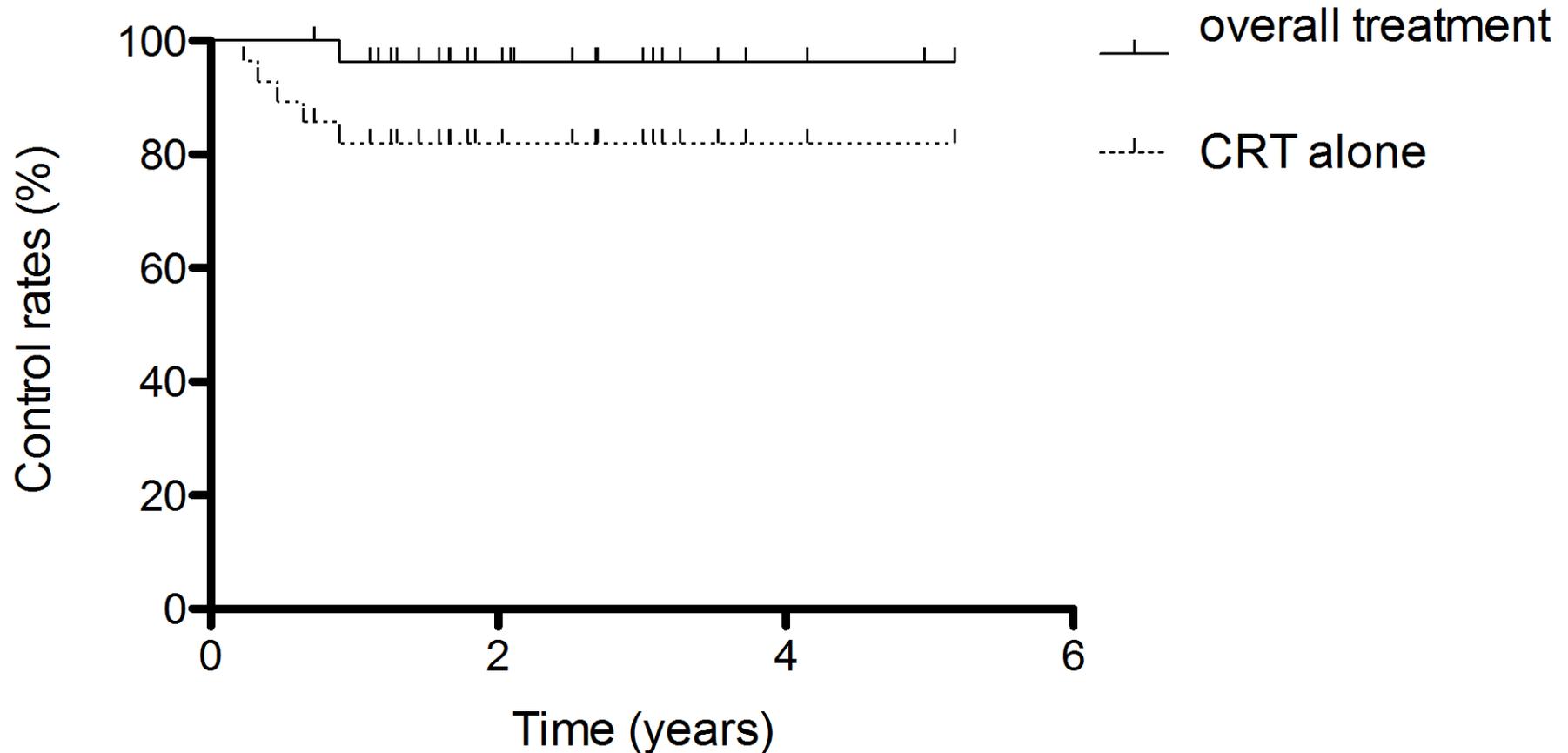


Figure 2. Kaplan Meier estimation of nodal control rates among 28 HNSCC patients with nodal metastasis. When viable tumor cells were observed in the surgical specimens obtained by neck dissection, the nodal control by weekly cisplatin chemoradiotherapy alone was defined as failure. The nodal control of overall treatment means including salvage by neck dissection.

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Fig 3.

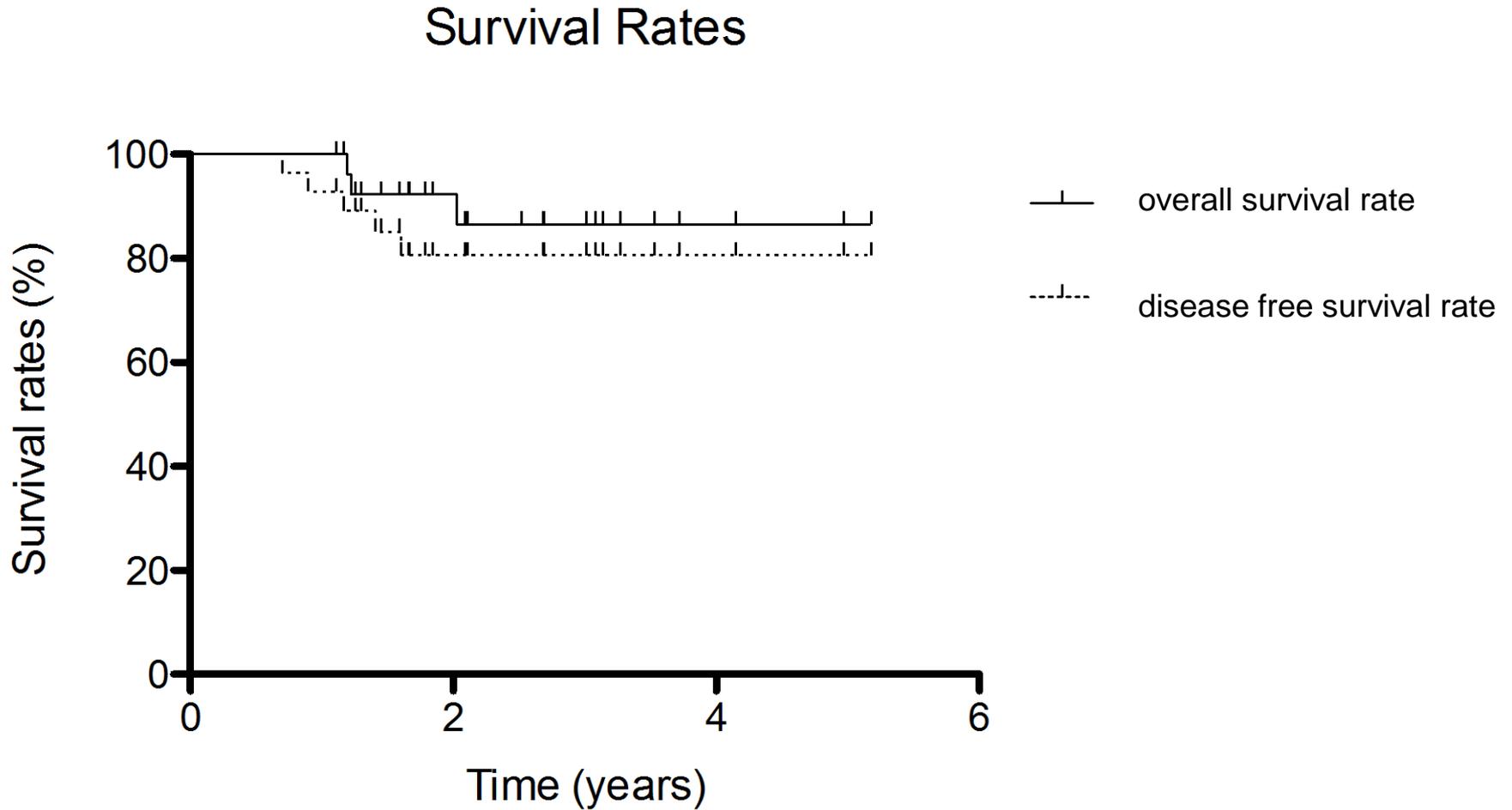


Figure 3. Kaplan Meier estimation of overall and disease free survival rates among 28 HNSCC patients with nodal metastasis.

Table 1. Patient Demographics

Characteristic	n
Total	28 (100%)
Gender	
Male	25 (89%)
Female	3 (11%)
Age, years	
Median	65
Range	47-75 (Ave. 63)
Follow up period, months	
Median	28
Range	8-62 (Ave. 30)
Primary site	
Oropharynx	12 (43%)
Hypopharynx	13 (46%)
Larynx	3 (11%)

Table 2. Distribution by T and N Classification

TN stage	No. of Patients					Total
	N1	N2a	N2b	N2c	N3	
T1	0	0	1	0	0	1
T2	1	0	10	1	1	13
T3	2	1	9	0	1	13
T4a	0	0	0	0	0	0
T4b	0	0	1	0	0	1
Total	3	1	21	1	2	28

Table 3. Toxicity (n=28)

Toxicity	Grade			
	1	2	3	4
Leucopenia	6	12	9	
Neutropenia	6	10	5	
Anemia	8	12	6	
Thrombocytopenia	7	2	1	
Febrile neutropenia			1	
Nausea/vomiting	5	2	2	
Mucositis		7	12	1
Renal dysfunction	10			
Liver dysfunction	2	2	2	
Dermatitis	3	6	13	
Fever	12	2	1	
Dysphagia	2	1	14	1
Hyponatremia	15		3	