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TITLE: The role of initial neck dissection for patients with node-positive oropharyngeal squamous cell carcinomas.

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Key words: regional recurrence, regional control, planned neck dissection, salvage neck dissection, chemoradiotherapy,

ABSTRACT

Background The current study sought to assess the role of initial neck dissection (ND) for patients with node-positive oropharyngeal squamous cell carcinomas (OPSCC).

Methods The data for 202 patients with previously untreated node-positive OPSCC were gathered from 12 institutions belonging to the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group. These patients were categorized into two groups, consisting of the initial ND group and the wait-and-see group, according to treatment policy.

Results Regional recurrence was observed in 17 of 93 patients undergoing initial ND, whereas, recurrent or persistent diseases were observed in 40 of 109 patients who did not undergo initial ND. The 4-year overall survival rates (OS) for the wait-and-see group and initial ND groups were 74.0% and 78.7%, respectively, and the 4-year regional control rates (RC) for each group were 77.6% and 84.9%. There were no significant differences in either OS or RC (p=0.3440 and p=0.2382, respectively). However, for patients with N3 disease, the 4-year OS of the initial ND group (100%) was favorable. For patients with N2a disease, the 4-year RC of the initial ND group was higher than that of the wait-and-see group statistically (100% vs 62.5%, p=0.0156).

Conclusions The role of initial ND was limited in patients with node-positive OPSCC. The treatment strategy not involving initial ND is considered feasible and acceptable when nodal evaluation after definitive radiotherapy or chemoradiotherapy is applied adequately. However, it is possible that initial ND improves outcomes in patients with resectable large-volume nodal disease.

INTRODUCTION

Head and neck cancers mostly arise from epithelial squamous cells in the mucosa in the upper aerodigestive tract with more than 500,000 new cases diagnosed worldwide each year [1]. The number of patients with oropharyngeal squamous cell carcinomas (OPSCC), in particular, has been increasing as infection with human papilloma virus (HPV) becomes more widespread.

The presence of regional metastasis is well known to be the most important factor affecting the prognoses for patients with head and neck cancer [2]. Neck dissection (ND) is most likely to be performed when primary disease is treated surgically for patients with regional metastasis. Traditionally, most patients with N2 or N3 disease have generally undergone initial ND consisting of upfront ND followed by concomitant chemoradiotherapy (CRT) or radiotherapy (RT), and planned ND regardless of nodal response [3,4]. However, in recent years, some investigators have advocated observation of the neck in patients initially diagnosed with N2-N3 disease, provided a complete response (CR) of regional disease is achieved after CRT or RT [5-7].

To date, there have been few multi-institutional reports evaluating the differences in outcome between the patients undergoing initial ND (upfront ND, planned ND, or simultaneous ND with primary resection) and those who did not undergo initial ND.

We, therefore, analyzed the overall survival rates and the regional control rates of patients with initial ND and those without initial ND, and evaluated the role of initial ND in patients with node-positive OPSCC.

METHODS

Patients

The data for 507 patients with previously untreated OPSCC between April 2005 and March 2007 were gathered from 12 institutions belonging to the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group (JCOG). The therapeutic strategy varied widely among the institutions. This study was a retrospective analysis, so the criteria for the selection of therapeutic modality were decided on the basis of the institutional policy or patient preference. The 160 patients with N0 and 47 patients treated with induction chemotherapy were excluded. A further 37 patients not

treated with curative intent were also excluded. In addition, 61 patients, who were observed for less than 24 months without regional recurrence, were excluded. The remaining 202 patients were eligible for this study.

In 109 patients, CRT or RT was performed without upfront or planned ND. If residual neck disease was observed after initial therapy, salvage ND was indicated. ND was not applied to patients with a CR of neck disease. This group, consisting of these 109 patients, was defined as the “wait-and-see” group. In the remaining 93 patients, ND was performed as the initial treatment. ND was performed simultaneously when primary disease was treated surgically in 80 of the 93 patients, and planned ND was performed regardless of nodal response after RT or CRT in 4 patients. Upfront ND followed by RT or CRT was performed in 9 patients. This group, consisting of these 93 patients, was defined as the “initial ND” group. The characteristics of each group are shown in table 1. There were no significant differences in any factor between the wait-and-see group and the initial ND group.

Time of assessment and evaluation method of regional diseases after initial treatment depended on the retrospective policy at each institution. This multi-institutional joint research has been representatively approved by the appropriate ethical committees of the National Hospital Organization Tokyo Medical Center, Tokyo, Japan, and written informed consent was obtained from all patients before entry into the study.

Statistics.

Associations between patient characteristics were tested using the chi-square test. The Kaplan-Meier method was applied for survival and control rates using JMP Pro 10.0.2 statistical software (SAS Institute, Cary, NC). The time of interest was the duration from the start of treatment to death or failure. Regional failure was defined as either radiographically suspicious or biopsy-proven recurrent nodal diseases that were not under control.

RESULTS

Details of initial treatment

The details of treatments in the wait-and-see group are shown in table 2. In

this group, RT alone, targeting both primary and regional disease, was performed in 56 patients. CRT was performed in 53 patients. The irradiation dose for patients in this group ranged from 22 to 77 Gy, with a median dose of 70 Gy. In the wait-and-see group, 93 patients (85.3%) achieved a CR for the primary tumor. Persistent primary diseases were observed in the remaining 16 patients. Among these 16 patients, 6 patients underwent salvage surgery for primary disease and 5 patients survived. The remaining 10 patients died of primary diseases without salvage surgery.

The details of treatments in the initial ND group are shown in table 3. The primary disease in 80 of the patients was treated by surgery. ND was performed simultaneously for these patients. In 35 of the 80 patients, post-operative RT was also performed. In this group, RT alone was performed for 8 patients and CRT was performed for 5 patients. These 13 patients underwent planned ND or upfront ND as the initial treatment. All 13 patients undergoing RT or CRT achieved a CR for primary disease after the completion of the initial treatment.

Regional disease and survival outcomes

Figure 1 and 2 indicates the treatment outcomes of the initial ND group and the wait-and-see group, respectively.

In 17 of 93 patients in the initial ND group (18.3%), regional recurrence was observed at a median of 8.2 months after the completion of initial treatment (range, 2.5 to 15.2 months) (Figure 1). In 6 of these 17 patients, salvage ND was performed at a median of 8.1 months after the initial treatment (range, 5.3 to 14 months). Regional diseases were successfully salvaged in 4 of the 6 patients (66.7%) by ND. One patient is alive with other regional diseases for more than 4 years after salvage ND. The remaining one patient died of unresectable regional disease at 6 months after the second neck dissection. In 11 patients with recurrent regional disease, salvage ND was not performed because of the presence of associated distant metastasis (n=4), radiotherapy was chosen (n=3), or the presence of unresectable recurrent disease (n=4). Two patients, who underwent additional radiotherapy targeting recurrent regional disease, were alive for 3.3 and 4.5 years after the recurrence. The remaining 9 patients died of neck diseases at a median of 18 months after the recurrence (range, 3 to 30 months).

In 40 of 109 patients in the wait-and-see group (36.7%), recurrent or persistent regional disease was observed at a median of 11 months after the completion

of initial therapy (range, 1 to 61 months) (Figure 2). Salvage ND was performed in 18 of these 40 patients. Regional diseases were successfully salvaged in 16 of 18 patients (88.9%) by ND. The remaining two patients died of unresectable regional disease at 24 months and 6 months, respectively, after the salvage ND. In 22 patients with recurrent or persistent regional disease, salvage ND was not performed because of the presence of associated distant metastasis (n=6), intended non-surgical treatment (additional radiotherapy; n=2, adjunctive chemotherapy; n=4) the presence of unresectable disease (n=6) or poor general condition (n=4). One patient undergoing additional radiotherapy remains alive with a CR of neck disease at 28 months after the additional treatment. Six patients remain alive with neck diseases at a median of 4 months after the recurrence (range, 4 to 61 months). The remaining 15 patients died of neck diseases at a median 10 months after the recurrence (range, 2 to 20 months).

Overall survival rates and regional control rates

The 4-year overall survival rates of the initial ND group and the wait and see group were 78.7% and 74.0%, respectively (Figure 3). Further, the 4-year regional control rates of each group were 84.9% and 77.6%, respectively (Figure 4). There were no significant differences in the overall survival rate or regional control rate between the two groups (p=0.3440 and p=0.2382, respectively).

Table 4 shows the overall survival and regional control rates according to N classification. For patients with N2a neck disease, there was significant difference in the 4-year regional control rates between the wait-and-see group and the initial ND group (62.5% vs 100%, p=0.0156). For patients with N3 neck disease, the 4-year overall survival rate of the initial ND group (100%) was favorable, though there was no significant difference statistically.

DISCUSSION

Our current study indicated regional control rates were 77.6-84.9% and that there was no significant difference between the initial ND group and the wait and see group, though some cases treated by RT alone without the initial ND were not expected to be curative. From this data, we could not conclude that the initial ND was better than the wait and see approach for patients with node-positive OPSCC. In the wait and see group, regional diseases were successfully controlled in 88.9% of all patients

undergoing salvage ND. Even when initial ND was not performed, salvage ND was feasible and beneficial after the recognition of residual or recurrent nodal disease. However, the evaluation of nodal response was crucial to the adequate performance of salvage ND. The use of computed tomography (CT) scans has been reported to be convenient and helpful in the evaluation of nodal response in terms of accuracy (negative predictive value: 88.5-94%) [8,9]. Some authors have also advocated the use of post-treatment fludeoxyglucose [F18]- positron emission tomography (PET) in determining the presence or absence of residual neck disease [5-7,10]. Goenka et al. analyzed the long-term regional control rate for patients with node-positive OPSCC treated by definitive CRT [11]. They reported that the regional control rate of patients without any sign of residual nodal disease on PET/CT scans or other modalities was 97.7%. This favorable data supports the use of a wait-and-see approach for patients with a CR of nodal disease. However, technical and timing issues with regard to the use of this modality in the assessment of treatment response during the early post-treatment period remain controversial.

N3 neck disease is generally associated with a higher rate of regional relapse [12]. However, N3 disease is infrequent and there have been few reports on the role of initial ND for patients with N3 head and neck cancer. Igidbashian et al. reported the outcome of 70 patients with N3 disease treated by CRT with or without ND [13]. They found that the disease-free survival rate of patients with ND was higher than that of patients without ND. Our data also indicated that the overall survival of N3 patients with initial ND was favorable. It is, therefore, possible that initial ND improves the survival rate for patients with resectable N3 disease. Further, we found that the regional control rates of N2a patients with initial ND were higher than those of patients without initial ND. We speculated that the initial ND could improve the outcome for patients with resectable large-volume nodal disease. However, the role of initial ND was considered limited as there were few patients with N2a or N3 diseases. There were no significant differences in overall survival or regional control between N2b-c patients with and without initial ND. The feasibility of a wait-and-see approach was confirmed for patients with N2b-c neck disease as well as for patients with N1 from our data.

The limitations of this study include the significant inequalities in the timing and the modalities for evaluating nodal response, institutional bias in treatment criteria, and its retrospective nature. It was reported that patients with HPV-positive OPSCC

showed an improved prognosis when compared to patients with HPV-negative tumors [14-17]. In this study, we did not detect any HPV DNA or p16 expression in primary tumor specimens. However, there were no significant differences in the rates of smoking or alcohol consumption between the initial neck dissection group and the wait-and-see group. Therefore, we considered the influence of HPV infection to be minimal in the current study.

In conclusions, the role of initial ND was not significant for patients with node-positive OPSCC. Treatment strategies that do not involve initial ND are considered feasible and acceptable when nodal evaluation after definitive RT or CRT is applied adequately. However, it is possible that initial ND improves outcomes in patients with resectable large-volume nodal disease.

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FIGURE LEGENDS

Figure 1. Treatment outcome in the initial neck dissection group

Figure 2. Treatment outcome in the wait-and-see group

Figure 3. Overall survival rates in the wait-and-see and initial neck dissection groups.

Figure 4. Regional control rates in the wait-and-see and initial neck dissection groups.

Table 1. Characteristics of patients in the wait-and-see and initial neck dissection groups.

Table 2. Details of treatments in the wait-and-see group

IA intra-arterial chemotherapy

Table 3. Details of treatments in the initial neck dissection group

IA intra-arterial chemotherapy

Table 4. Overall survival and regional control rates according to N classification

OS overall survival, *RC* regional control, *ND* neck dissection

Figure 1

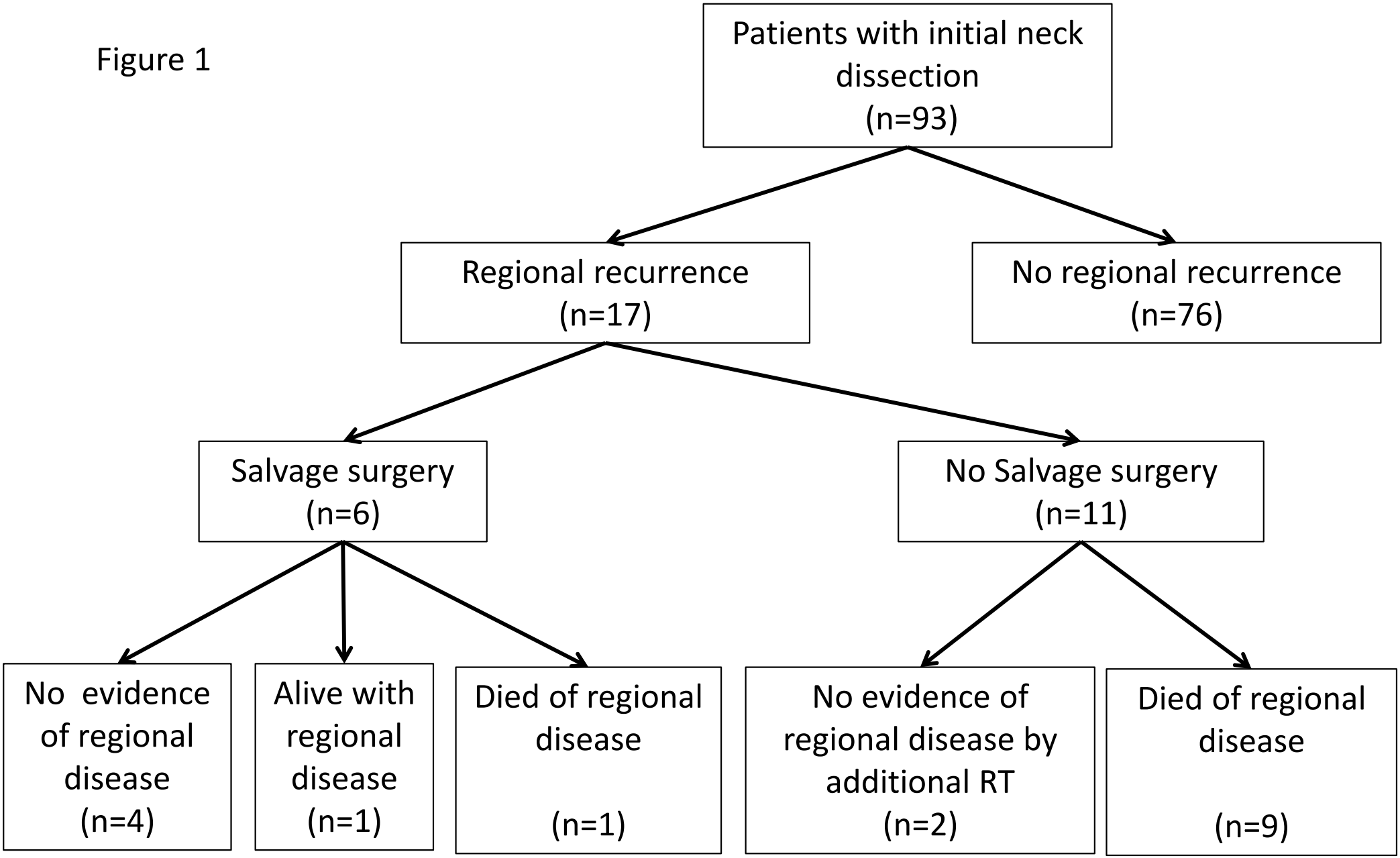
Patients with initial neck dissection (n=93)
Regional recurrence (n=17)
No regional recurrence (n=76)
Salvage surgery (n=6)
No Salvage surgery (n=11)
No evidence of regional disease (n=4)
Alive with regional disease (n=1)
Died of regional disease (n=1)
No evidence of regional disease by additional RT (n=2)
Died of regional disease (n=9)

Figure 2

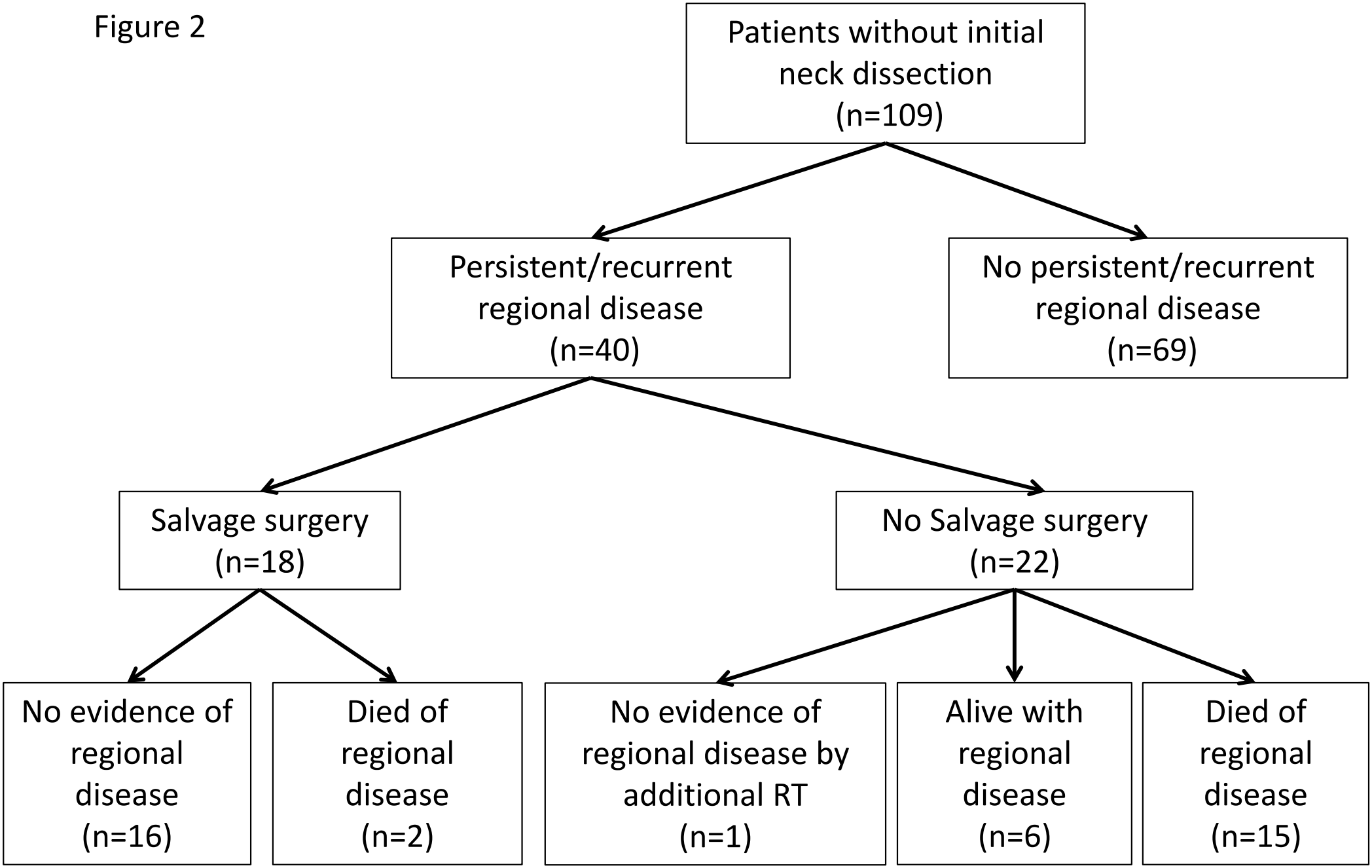
Patients without initial neck dissection (n=109)
Persistent/recurrent regional disease (n=40)
No persistent/recurrent regional disease (n=69)
Salvage surgery (n=18)
No Salvage surgery (n=22)
No evidence of regional disease (n=16)
Died of regional disease (n=2)
No evidence of regional disease by additional RT (n=1)
Alive with regional disease (n=6)
Died of regional disease (n=15)

Figure 3

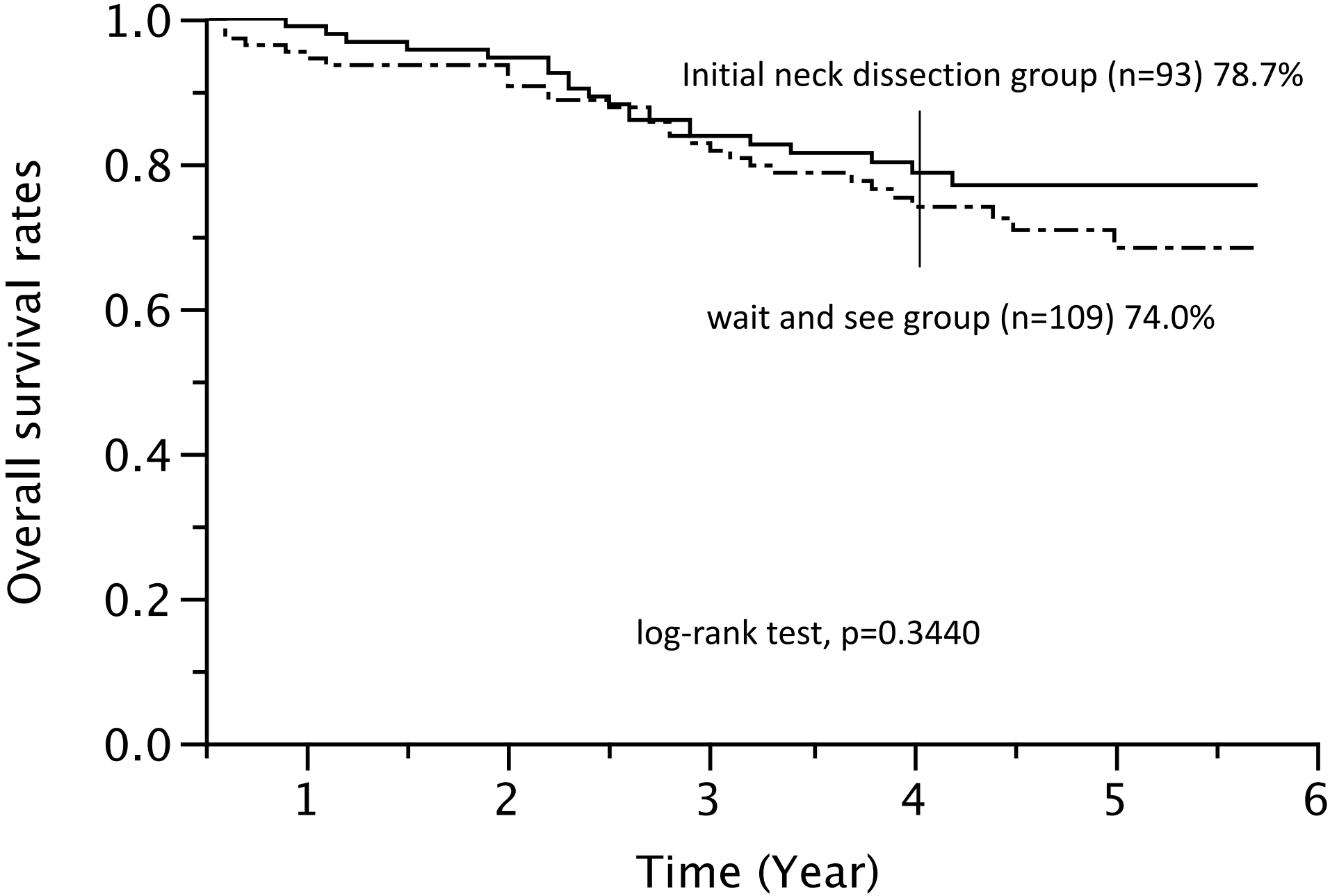
1.0
0.8
0.6
0.4
0.2
0.0
Overall survival rates
1
2
3
4
5
6
Time (Year)
Initial neck dissection group (n=93) 78.7%
wait and see group (n=109) 74.0%
log-rank test, p=0.3440

Figure 4

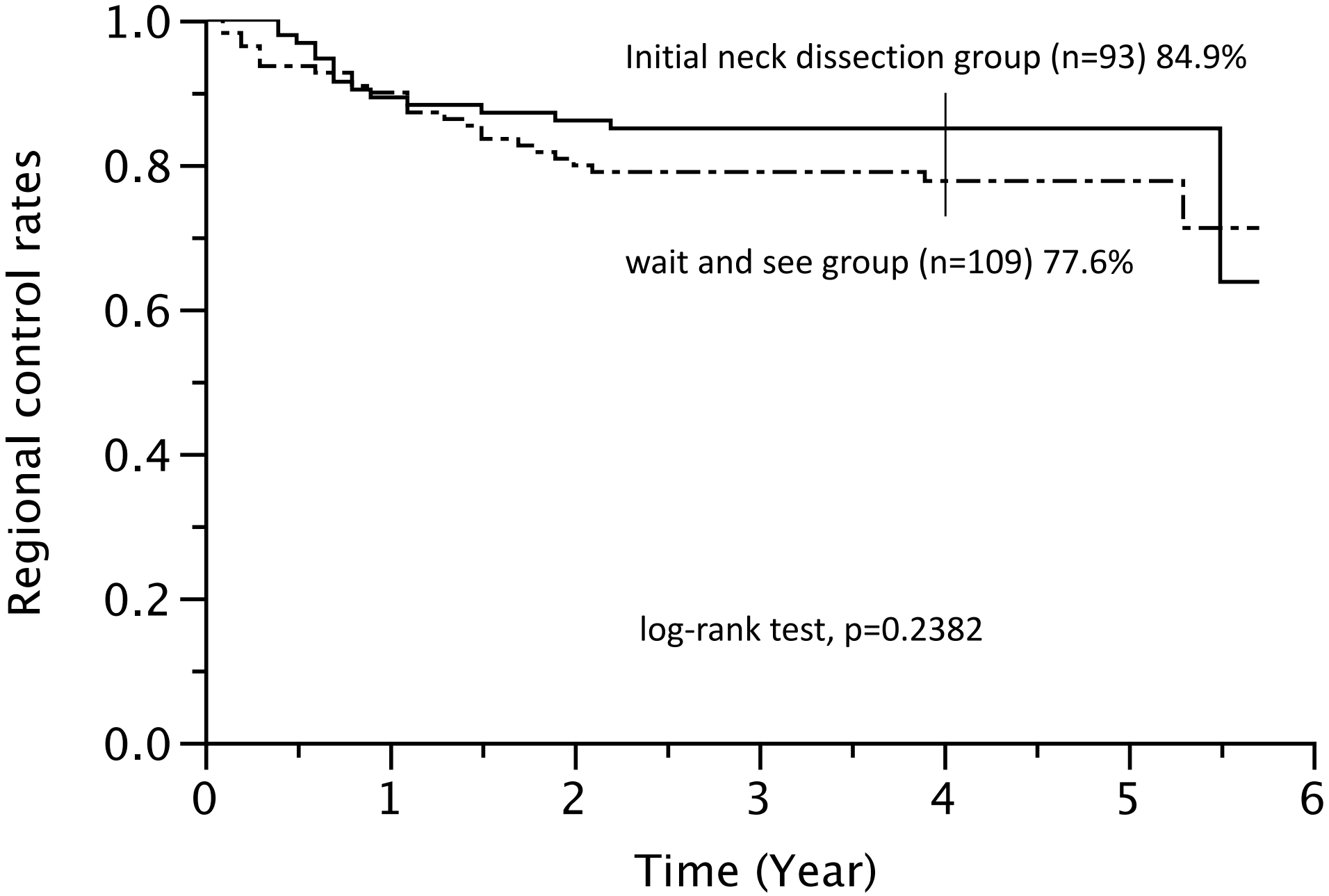
1.0
0.8
0.6
0.4
0.2
0.0
Regional control rates
0
1
2
3
4
5
6
Time (Year)
Initial neck dissection group (n=93) 84.9%
wait and see group (n=109) 77.6%
log-rank test, p=0.2382

Table 1. Characteristics of patients in the wait-and-see and initial neck dissection

Variable	No. of Patients (%)		*p* value
	Wait-and-see group (n=109)	Initial neck dissection group (n=93)	
Age, years			
<62	54 (49.5)	49 (52.7)	0.655641
>63	55 (50.5)	44 (47.3)	
Gender			
Male	93 (85.3)	77 (82.8)	0.624162
Female	16 (14.7)	16 (17.2)	
Subsite			
Lateral wall	80 (73.4)	56 (60.2)	
Anterior wall	23 (21.1)	31 (33.3)	
Posterior wall	4 (3.7)	0 (0)	
Upper wall	2 (1.8)	6 (6.5)	
T classification			
1-2	71 (65.1)	54 (58.1)	0.3022279
3-4	38 (34.9)	39 (41.9)	
N classification			
1	16 (14.7)	17 (18.3)	
2a	16 (14.7)	13 (14.0)	
2b	43 (39.4)	38 (40.9)	
2c	25 (22.9)	19 (20.4)	
3	9 (8.3)	6 (6.4)	
Smoking behavior			
present	86 (78.9)	76 (81.7)	0.6159961
absent	23 (21.1)	17 (18.3)	
Daily alcohol consumption			
present	84 (77.1)	69 (74.2)	0.6351948
absent	25 (22.9)	24 (25.8)	
Follow-up of survivors, years			
Median (range)	4.6 (0.9-5.7)	4.5 (2.3-5.7)	

groups.

Table 2. Details of treatments in the wait-and-see group

Variable	No. of Patients (%)
Radiation alone	56 (52.8)
Concomitant chemoradiotherapy	53 (48.6)
Concomitant chemotherapy regimens	
Cisplatin, 5FU	23
Cisplatin	17
Docetaxel	7
S1	2
Nedaplatin, 5FU	1
Cisplatin (IA)	3
Salvage neck dissection	18 (16.5)

IA intra-arterial chemotherapy

Table 3. Details of treatments in the initial neck dissection group

Variable	No. of Patients (%)
Surgery for primary disease	80 (86.0)
Transoral surgery	21
Open surgery with total laryngectomy	15
Open surgery without total laryngectomy	44
Radiation for primary disease	13 (14.0)
Radiation alone	8
Concomitant chemoradiotherapy	5
Concomitant chemotherapy regimens	
Cisplatin, 5FU	3
Cisplatin	1
Cisplatin (IA)	1
Neck Dissection	
Ipsilateral	65 (69.8)
Bilateral	28 (30.1)

IA intra-arterial chemotherapy

Table 4. Overall survival and regional control rates according to N classification

Classification	Group	No. of patients	4yr OS	*p* value	4yr RC	*p* value
N1	Wait-and-see	16	68.2%		93.8%	
	Initial ND	17	82.4%	0.2195	94.1%	0.9476
N2a	Wait-and-see	16	74.6%		62.5%	
	Initial ND	13	100%	0.0577	100%	0.0156
N2b	Wait-and-see	43	82.8%		86.1%	
	Initial ND	38	76.8%	0.5327	86.8%	0.8696
N2c	Wait-and-see	25	69.4%		76.0%	
	Initial ND	19	56.4%	0.3156	68.4%	0.6817
N3	Wait-and-see	9	50.8%		37.0%	
	Initial ND	6	100%	0.0515	66.7%	0.3164

OS overall survival, *RC* regional control, *ND* neck dissection