Title: The role of prophylactic neck dissection and tumor thickness evaluation for patients with cN0 tongue squamous cell carcinoma

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Running title: Prophylactic neck dissection and tumor thickness evaluation for cN0 tongue carcinomas.

Financial support: None.

Compliance with Ethical Standards:

Funding: This study was supported in part by Health and Labour Sciences Research Grants for Clinical Cancer Research (H22-017 and H26-141) from the Ministry of Health, and Labour and Welfare of Japan, the National Cancer Center Research and Development Fund (23-A-21 and 26-A-4) of Japan.

Conflict of Interest: no conflict exists: Author Nayuta Tsushima, declares that he has no conflict of interest. Author Tomohiro Sakashita, declares that he has no conflict of interest. Author Akihiro Homma, declares that he has no conflict of interest. Author Hiromitsu Hatakeyama, declares that he has no conflict of interest. Author Satoshi Kano, Author Takatsugu Mizumachi,declares that he has no conflict of interest. Author Tomohiko Kakizaki, declares that he has no conflict of interest. Author Takayoshi Suzuki declares that he has no conflict of interest. Author Satoshi Fukuda, declares that he has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the

study.

Acknowledgement:

This study was supported in part by Health and Labour Sciences Research Grants for Clinical Cancer Research (H22-017 and H26-141) from the Ministry of Health, and Labour and Welfare of Japan, the National Cancer Center Research and Development Fund (23-A-21 and 26-A-4) of Japan.

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Purpose. Prophylactic neck dissection (PND) for patients with clinically N0 (cN0) tongue carcinoma remains controversial. We assessed the efficacy of PND for patients with cN0 tongue squamous cell carcinoma (SCC) and investigated the prognostic role of tumor thickness as assessed by diagnostic imaging in predicting the risk of nodal micrometastasis or late nodal recurrence.

Methods. Eighty-eight patients with cN0 tongue carcinomas underwent surgical treatment. Tumor thickness was measured from magnetic resonance (MR) images or computed tomography (CT) scans.

Results. The overall survival rates of patients with or without PND were 94% and 81%, respectively (p=0.2857). MR images or CT scans were available for 68 patients. A tumor thickness ≧10mm or ≧5mm did not increase the probability of nodal metastasis, with late nodal metastasis observed in 15% of patients with graphically undetected small tumors.

Conclusions. PND appears to have the potential to improve overall survival for patients with cN0 tongue SCC. Careful follow-up management or PND is considered to be needed regardless of tumor thickness in the pre-treatment evaluation.

Introduction

Oral cancer is sixth most common cancer in the world, accounting for 3% of all cancer [1]. Tongue squamous cell carcinoma (SCC) is the most common malignancy of the oral cavity [2], and nodal metastasis has been reported as one of the prognostic factors for patients with tongue SCC [3].

Prophylactic neck dissection (PND) for patients with cN0 tongue cancer remains controversial. Economic loss and patient burden associated with redundant surgeries have been problematic, although a massive phase III study in India has proven that PND improves overall survival [4]. We evaluated the efficacy of PND for patients with clinically N0 (cN0) tongue SCC, and investigated the prognostic role of tumor thickness in predicting the risk of nodal micrometastasis or late nodal recurrence prior to treatment.

Material and methods

Patients. Between January 2005 and December 2014, 134 patients with tongue SCC were treated by surgery in our department. Ninety-three of these 134 patients were diagnosed as cN0. Five patients who had sentinel node biopsy were excluded, with the remaining 88 patients eligible for this study. Approval for this study was obtained from the Institutional Review Board of Hokkaido University. Completion of the survey was regarded as implied consent for participation. Patient characteristics are shown in Table 1.

Pre-treatment. T classification of the tongue tumors was evaluated by clinical examination and enhanced magnetic resonance (MR) imaging, where possible. Plain MR images or computed tomography (CT) scans were acceptable for patients who could not tolerate enhanced MR imaging. The thickness of the tongue tumors was evaluated from the surface of the tumor to the deepest portion from the MR image or CT scan. N classification was evaluated by clinical examination and ultrasonography of the neck. CT scans or MR images were also used for evaluation of N classification where available.

The T classification is shown in Table 1. Thirty-three of 70 patients (47%) in the observation group had primary tumors that were classified as T2 or greater. On the other hand, all patients in the PND group had primary tumors that were classified as T2 or T3. There was significant difference in primary tumor status between the observation group and the PND group ($p<0.001$).

Surgical treatment and type of neck dissection. All 88 patients treated by partial glossectomy with or without free flap reconstruction. Primary tumors were resected with a 1.5-2.0 cm surgical margin. Surgical margin specimens were evaluated by frozen section histological analysis. A PND was intended

on a case-by-case basis. Therapeutic ND was also indicated for patients developing late nodal recurrence. The extent of PND was level I, II, and III, with non-lymphatic structures preserved. The extent of therapeutic neck dissection was level I, II, III, IV, and V, with the preservation of non-lymphatic structures also intended, where possible. Tumor thickness was confirmed by histological analysis.

Follow-up management. Patients were usually monitored monthly for recurrence in the first year, every couple of months in the second year, and every 6 or 12 months thereafter until death or data censoring. CT scans, MR imaging or US was routinely performed once every three months in the first year, and every 6 or 12 months thereafter. If recurrent primary disease was suspected, biopsy was attempted and salvage surgery was indicated by the presence of tumor cells. If recurrent regional disease was observed, therapeutic ND was indicated immediately.

Statistics. An unpaired t-test or chi-squared test was applied for the comparison of values for two unpaired groups. The Kaplan-Meier method was used for the calculation of survival rates and probability of nodal metastasis using JMP Pro 12.0.1 statistical software (SAS Institute, Cary, NC). Time of interest was the period from the start of treatment to death or failure. The log-rank test was applied to compare the survival rates and probability of nodal metastasis between two groups.

Results

Types of neck management. Seventy patients (75%) were treated by partial glossectomy without prophylactic neck dissection. These 70 patients were classified as the observation group. Eighteen patients (19%) were treated by partial glossectomy or hemiglossectomy with associated prophylactic neck dissection. These 18 patients were classified as the PND group. In 7 of these 18 patients, free flap reconstruction was performed to improve eating function.

Clinical outcomes. Surgical margins were confirmed as tumor free by histological analysis in all patients. Fifteen of 70 patients (21%) in the observation group had late nodal metastasis. Fourteen of these 15 patients underwent therapeutic ND. Although one patient had level IV lymph node metastasis on the non-affected side, no level IV metastatic lymph nodes were found on the affected side. Nine patients survived without any evidence of disease. The five-year survival rate for the observation group was 81% and the disease-free survival rate was 62%.

Nine of 18 patients (50%) in the PND group were positive for lymph node metastasis. Three of the 18 patients (17%) in the PND group had late neck recurrence in the untreated neck area. Occult neck

metastasis was observed during PND in all three of these patients. Only one of these three patients underwent additional neck dissection, and he survived without any evidence of disease. The other two patients did not undergo additional neck dissection. One patient died of neck disease and the other patient remains alive with disease. Overall, 24 of 88 (27%) had late nodal metastasis.

The number of patients with occult neck metastasis by T stage was 4 (11%) for T1, 20 (42%) for T2 and 0 for T3, respectively.

The five-year overall survival rate ~~of~~ for the PND group was 94% and the disease-free survival rate was 83%. There was no significant difference in the overall survival rate between the observation group and the PND group (p=0.2857, Fig. 1). Similarly, there was no significant difference in the disease-free survival rate (p=0.1572, Fig. 2).

Pre-treatment evaluation of tumor thickness. In 72 patients, MR images and/or CT scans were performed to evaluate tongue tumor thickness. In four of 72 patients, the tongue tumor was undetectable because of artifacts. These four cases were excluded from our evaluation of the association between tumor thickness and nodal metastasis. Thirty-nine patients were evaluated by enhanced MR images, 7 patients were evaluated by plain MR images and 22 patients were evaluated by CT scans. In 52 of 68 patients (76%), the tongue tumor was detectable with a mean of thickness was 9 mm (range, 4-28 mm). In the remaining 16 patients (24%), the tongue tumor was undetectable. The probabilities of nodal metastasis in patients with a tumor thickness of ≥10 mm and in those with a tumor thickness of <10 mm thickness (including those with undetectable tumors) were 24% and 31%, respectively (p=0.6665, Fig. 3). In addition to, patients with a tumor thickness of ≥5 mm and in those with a tumor thickness of <5 mm thickness were 35% and 16%, respectively (p=0.1447, Fig. 4). Further, the probabilities of nodal metastasis in patients with a detectable tumor and those with an undetectable tumor were 32% and 15%, respectively (p=0.1412, Fig. ~~3~~5)

Histological evaluation of tumor thickness.

Primary tumor specimens were available for histological evaluation of tumor thickness in 66 patients. Tumor thickness ranged from 0.4 to 18 mm, with a median tumor thickness of 4 mm. When we set the cut off value for tumor thickness as evaluated histologically at 6 mm, there was a statistically significant difference in the rate of occult neck metastasis. The probabilities of nodal metastasis in patients with a tumor thickness of ≥6 mm and in those with a tumor thickness of <6 mm thickness were 48% and 20%, respectively (p=0.0105, Fig. 6). The mean histological tumor thickness in the observation group and PND group were 4.7mm (range, 3-15 mm) and 7 mm (range, 0.4-18 mm), respectively. The correlation

coefficient for tumor thickness by diagnostic imaging and histological evaluation was 0.7262 ($p<0.001$, Fig. 7).

Discussion

The ability to control tongue SCC is closely related to the extent of the primary tumor and the state of the regional lymph nodes [3]. Tongue cancer carries the highest rate of nodal metastasis among all intraoral cancers [5].

In this retrospective study, treatment strategy was decided on the basis of disease status as well as in consideration of the patient's general condition or patient's wishes. Consequently, the tumor status of the PND group was generally more advanced than that in the observation group. Although the difference was not statistically significant, we nevertheless observed a tendency toward a higher survival rate in the PND group. Similar to previous studies, it is thought that PND may improve the treatment outcome for cN0 patients.

Previous studies have reported and, in some cases, anticipated that thicker tumors are more likely to be associated with occult neck metastasis [6]. In the current study, although thicker tumors had a higher probability of occult neck metastasis (Fig.6), 16% of patients with graphically undetected small tumors demonstrated late nodal metastasis. In addition, there was no significant difference when we set the cut off value for tumor thickness as measured by diagnostic imaging at 10 mm or 5 mm. Christine also reported that MR imaging has some predictive value in estimating tumor thickness, although it is not possible to safely determine the need for neck dissection from either MRI staging of neck metastasis or tumor thickness [7]. Some molecular biomarkers offer potential risk stratification in judging the risk of metastasis [8]; however, these biomarkers have not had a clinical impact to date.

The extent of PND remains controversial. Huang suggested that supraomohyoid neck dissection is sufficient based a total of 37 patients who received radical neck dissection as PND, among whom only 2 patients were found to have positive lymph nodes in level IV [9]. In the current study, the extent of the PND was level I, II, and III. Although 3 patients in the PND group had late neck recurrence, they did not have any metastatic lymph nodes in level IV. The extent of therapeutic neck dissection, on the other hand, was level I, II, III, IV, and V. Although one patient had level IV lymph node metastasis on the non-affected side, no metastatic lymph nodes were found on the in level IV on the affected side. In consideration of the probability of metastasis, we also think that level IV neck dissection can be omitted for cN0 patients.

D'Cruz showed that patients undergoing PND have higher rates of overall and disease-free survival than do the observation group [4]. On the other hand, Anthony reported that there was no significant difference

in the 5-year disease free survival rate between the observation group and PND group [10]. Some studies have suggested that late neck recurrence is associated with a greater number of positive nodes and a higher incidence of extracapsular spread (ECS); as a consequence, the salvage rates of patients experiencing neck recurrence were poor [11]. Godden reported that 96% of patients with late neck recurrence had ECS [12]. In the current study, fifteen patients in the PND group developed late neck recurrence, with fourteen of them treated by therapeutic neck dissection. ECS was detected in 4 cases (29%), and 9 patients (60%) were alive at the end of the follow-up period. Meanwhile, no ECS was detected in the PND group. Although the rate of ECS in the therapeutic neck dissection group was lower and the rate of patients who were treated by surgery was higher than in previous studies, the salvage rate was not as pleasing. It is presumed that the prognosis for patients with late nodal metastasis is not always improved if they are treated by therapeutic neck dissection.

The advantages of observation are in the avoidance of unnecessary surgery and associated complications. It is reported that, in general, twenty to thirty percent of clinically negative necks in early stage tumors have metastasis [13]. In other words, about 70 to 80 % of such patients do not require PND. These rates are similar to those observed in the current study. One of the advantages of PND is to prevent late lymph node metastasis. In addition to, this technique allows correct neck staging and determination of the need for adjuvant therapies. Consequently, patients can be treated with an appropriate adequate post-operative therapy on the basis of pathological evaluation. Bernier reported that the addition of concomitant cisplatin to postoperative radiotherapy improves outcomes in patients with ECS who are medically fit to receive chemotherapy [14].

Interval elective neck dissection is recommended by Fakih [15]. This method allow for accurate measurement of tumor thickness from permanent sections. Patients at high risk of occult neck metastasis are treated by neck dissection as a second surgery. Second surgery is performed at 8-12 weeks after glossectomy. This method can avoid some redundant surgeries if patients are amenable to undergoing two surgical procedures. Further studies are also needed to compare clinical outcomes between these novel approaches and standardized PND.

Conclusions

Prophylactic neck dissection is thought to improve overall and disease-free survival for patients with N0 tongue cancer. Although the pre-treatment evaluation of tumor thickness has some predictive value in estimating histological tumor thickness, it is not a reliable method for predicting the risk of nodal micrometastasis or late nodal recurrence in patients with cN0 tongue cancer. There were no significant differences when we set the cut off value for tumor thickness as measured by diagnostic imaging at 10

mm or 5 mm. Further, it is worthy of note that 16% of patients with a tumor that was undetectable in MR images or CT scans had late neck recurrence. Careful follow-up management or prophylactic neck dissection is considered to be needed regardless of the tumor thickness based on pre-treatment evaluation.

FIGURE LEGENDS

Table 1. The details of the prophylactic neck dissection group and the observation group.

Figure 1. Overall survival rates of the prophylactic neck dissection group and the observation group.

Figure 2. Disease-free survival rates of the prophylactic neck dissection group and the observation group.

Figure 3. The probabilities of nodal metastasis in patients with a detectable tumor and those with an undetectable tumor.

Figure 4. The probabilities of nodal metastasis in patients with a tumor thickness of 5 mm or more and those with a tumor of less than 5 mm (including undetectable tumors).

Figure 5. The probabilities of nodal metastasis in patients with a detectable tumor and those with an undetectable tumor.

Figure 6. The probabilities of nodal metastasis in patients with a histological tumor thickness of 6 mm or more and those with a tumor of less than 6 mm.

Figure 7. Scatter plot: Diagnostic imaging tumor thickness and histological tumor thickness. The broken line is the best fitting regression line.

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Table 1

		Observation group	the PND group	p value
No. of patients		70	18	
Sex	Male	40	11	
	Female	30	7	0.7610
Median age (years old, range)		61.5 (32-82)	65 (25-95)	0.2871
T classification	T3	2	2	
	T2	31	16	
	T1	37	0	
	The proportion of T≧2	47%	100%	<0.001

Figure 1

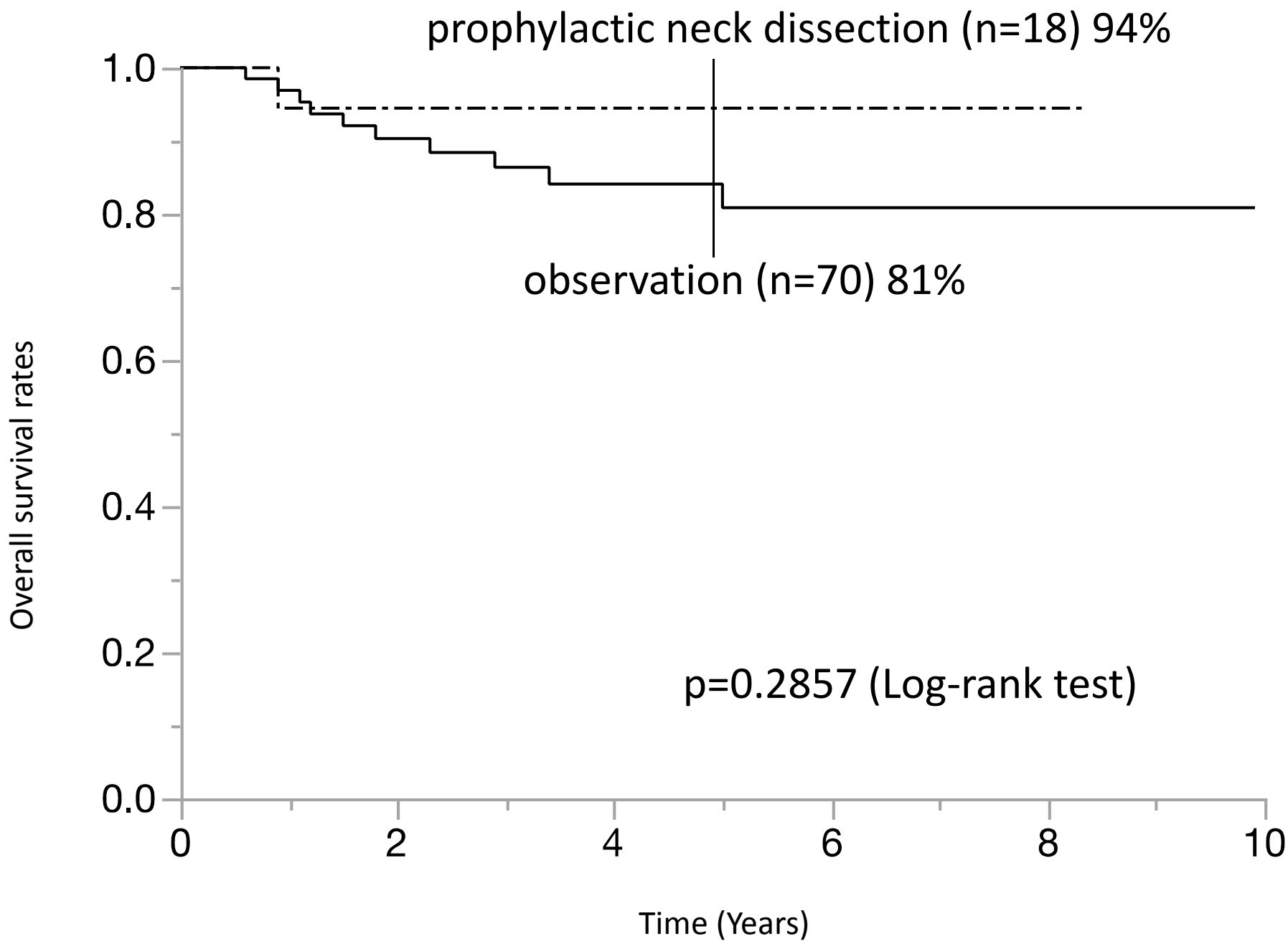

prophylactic neck dissection (n=18) 94%
observation (n=70) 81%
p=0.2857 (Log-rank test)
Overall survival rates
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Time (Years)

Figure 2

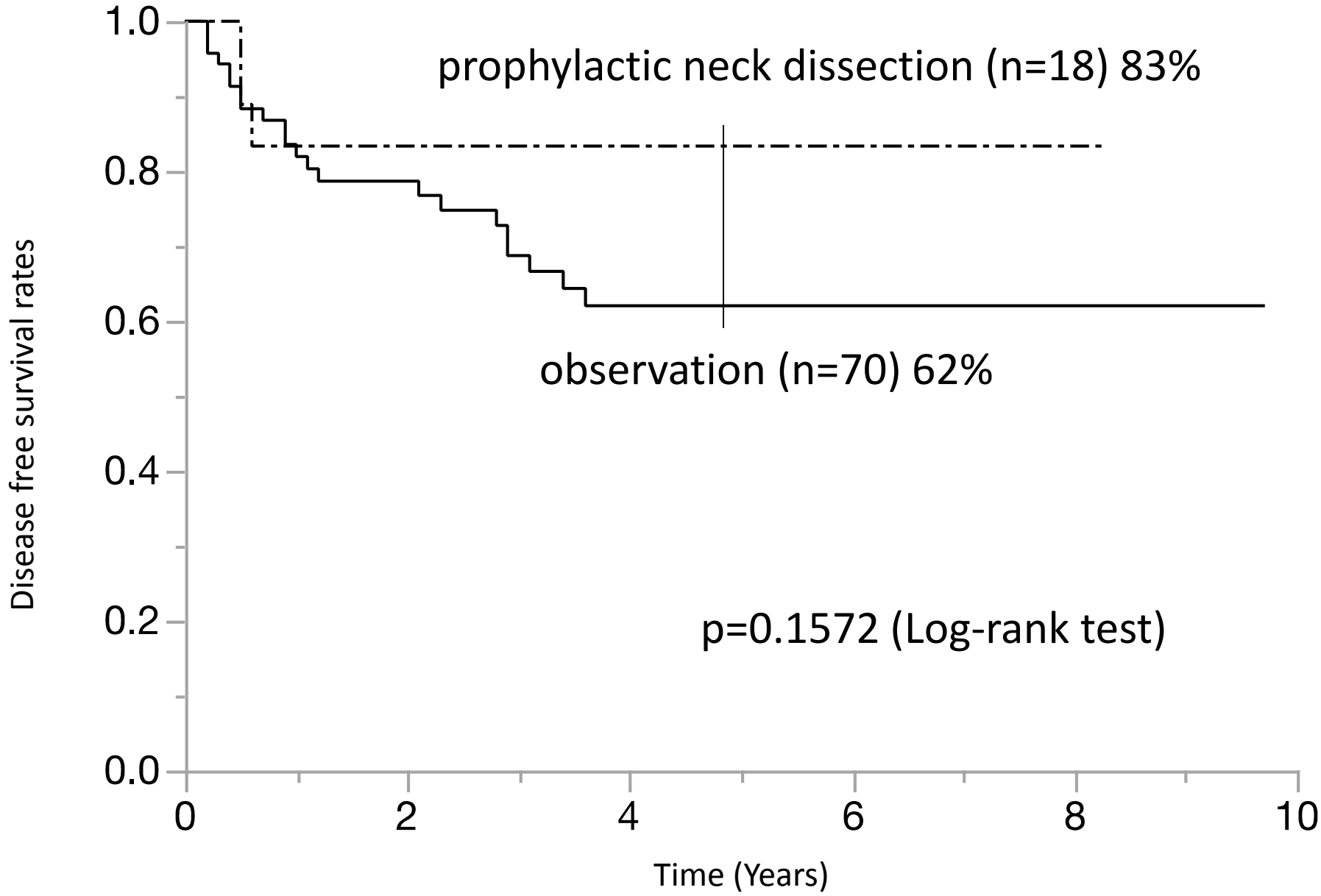

1.0
0.8
0.6
0.4
0.2
0.0
Disease free survival rates
prophylactic neck dissection (n=18) 83%
observation (n=70) 62%
p=0.1572 (Log-rank test)
0
2
4
6
8
10
Time (Years)

Figure 3

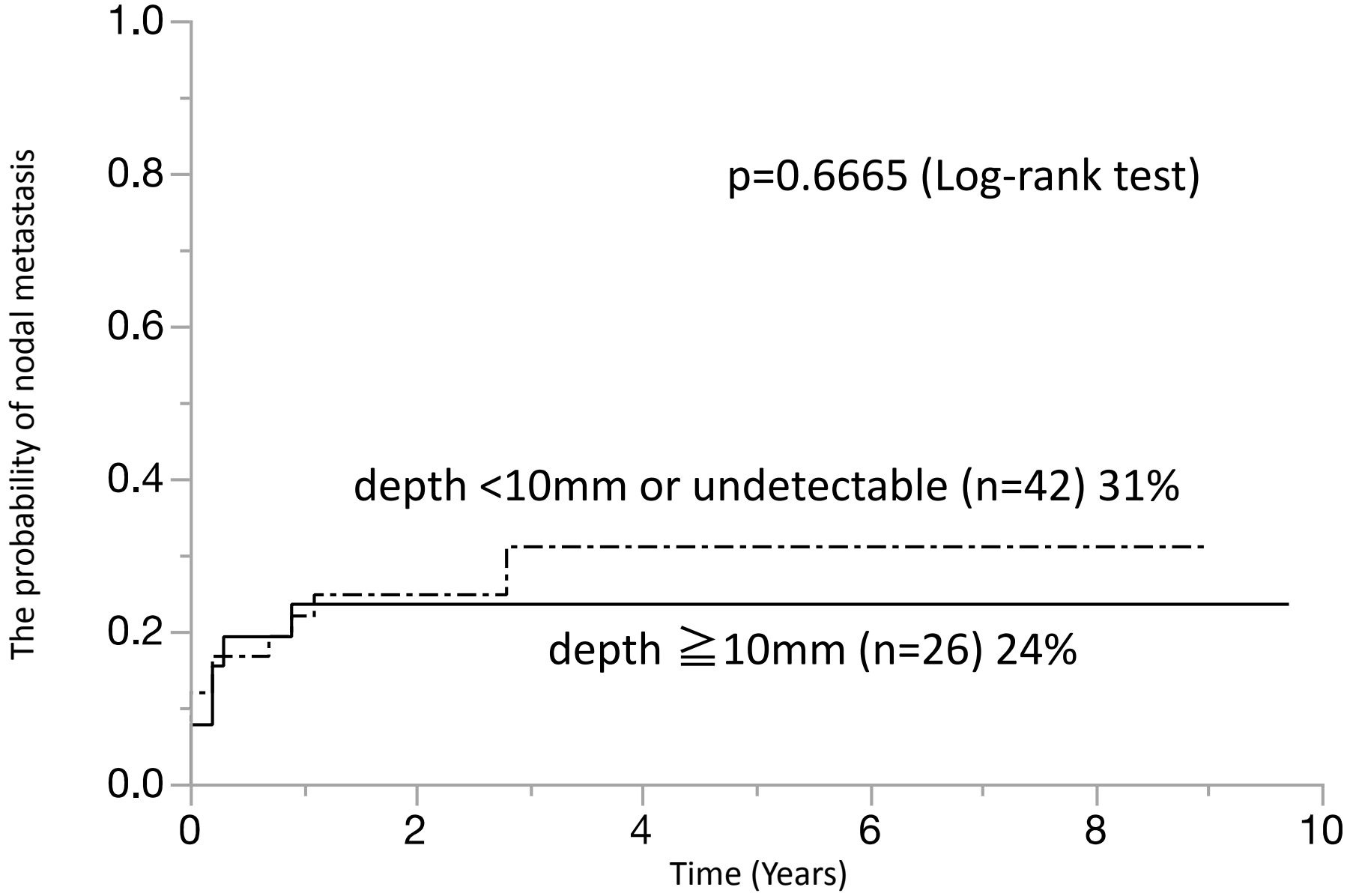

1.0
0.8
0.6
0.4
0.2
0.0
The probability of nodal metastasis
p=0.6665 (Log-rank test)
depth <10mm or undetectable (n=42) 31%
depth ≧10mm (n=26) 24%
0
2
4
6
8
10
Time (Years)

Figure 4

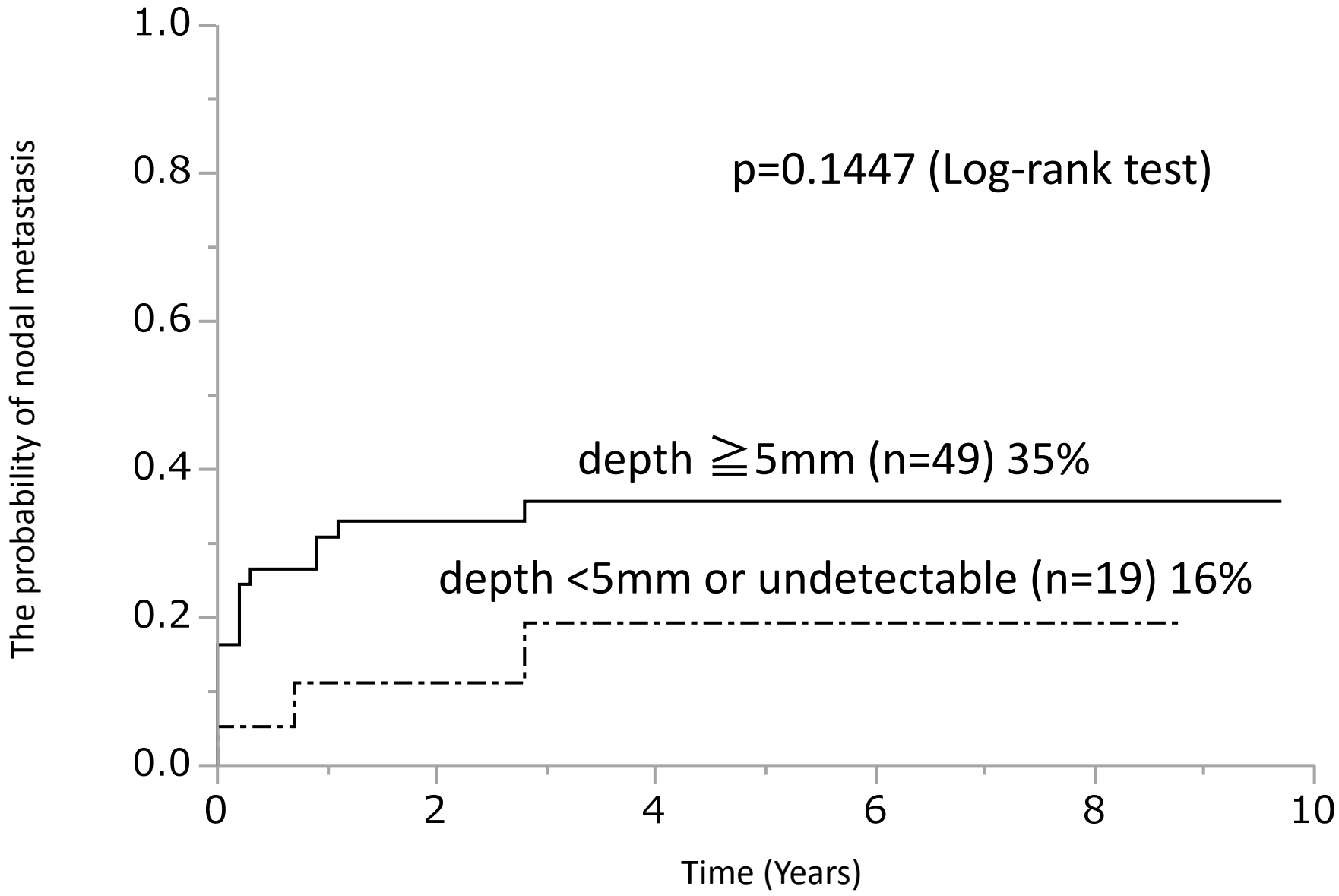

1.0
0.8
0.6
0.4
0.2
0.0
The probability of nodal metastasis
p=0.1447 (Log-rank test)
depth ≧5mm (n=49) 35%
depth <5mm or undetectable (n=19) 16%
0
2
4
6
8
10
Time (Years)

Figure 5

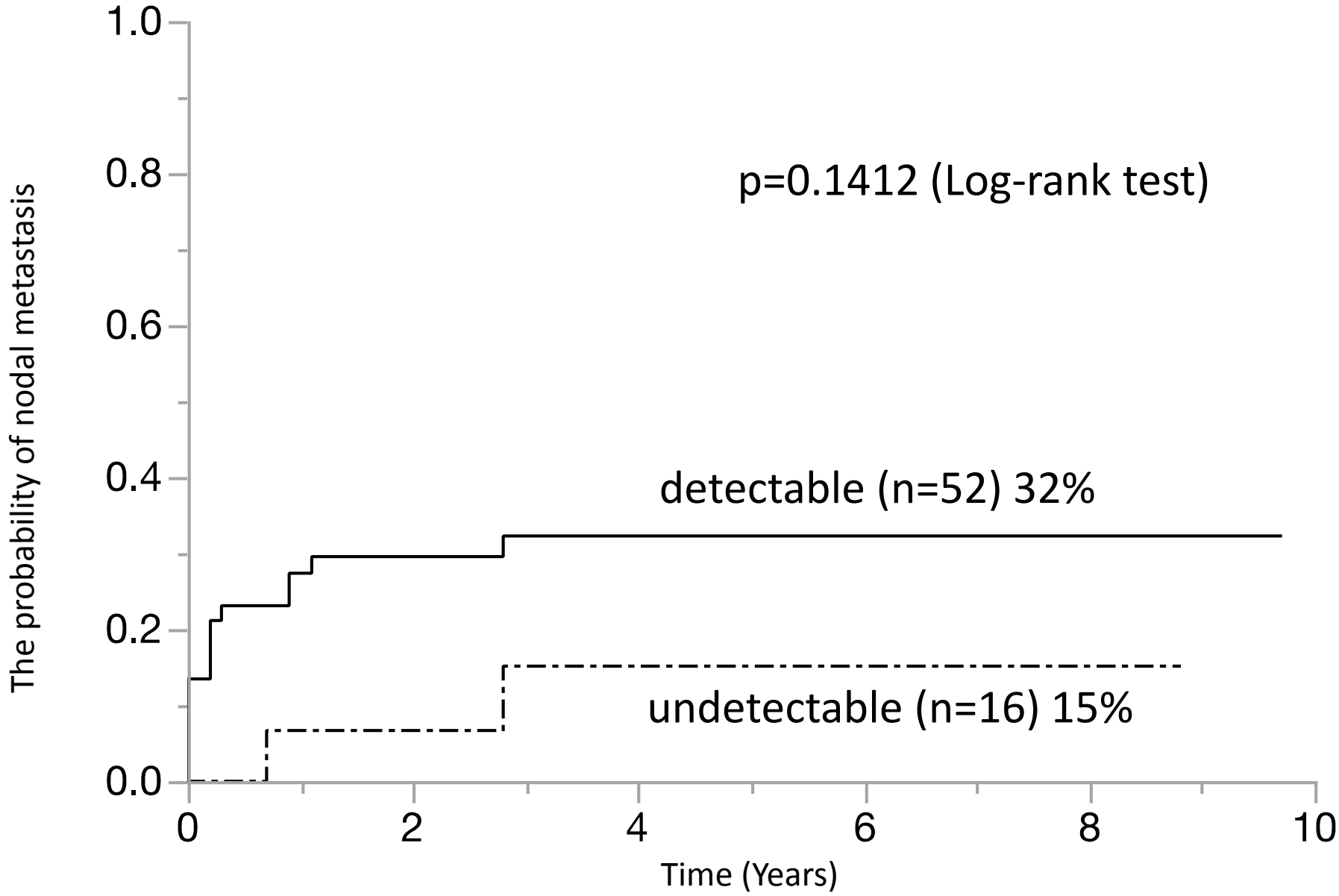

1.0
0.8
0.6
0.4
0.2
0.0
The probability of nodal metastasis
p=0.1412 (Log-rank test)
detectable (n=52) 32%
undetectable (n=16) 15%
0
2
4
6
8
10
Time (Years)

Figure 6

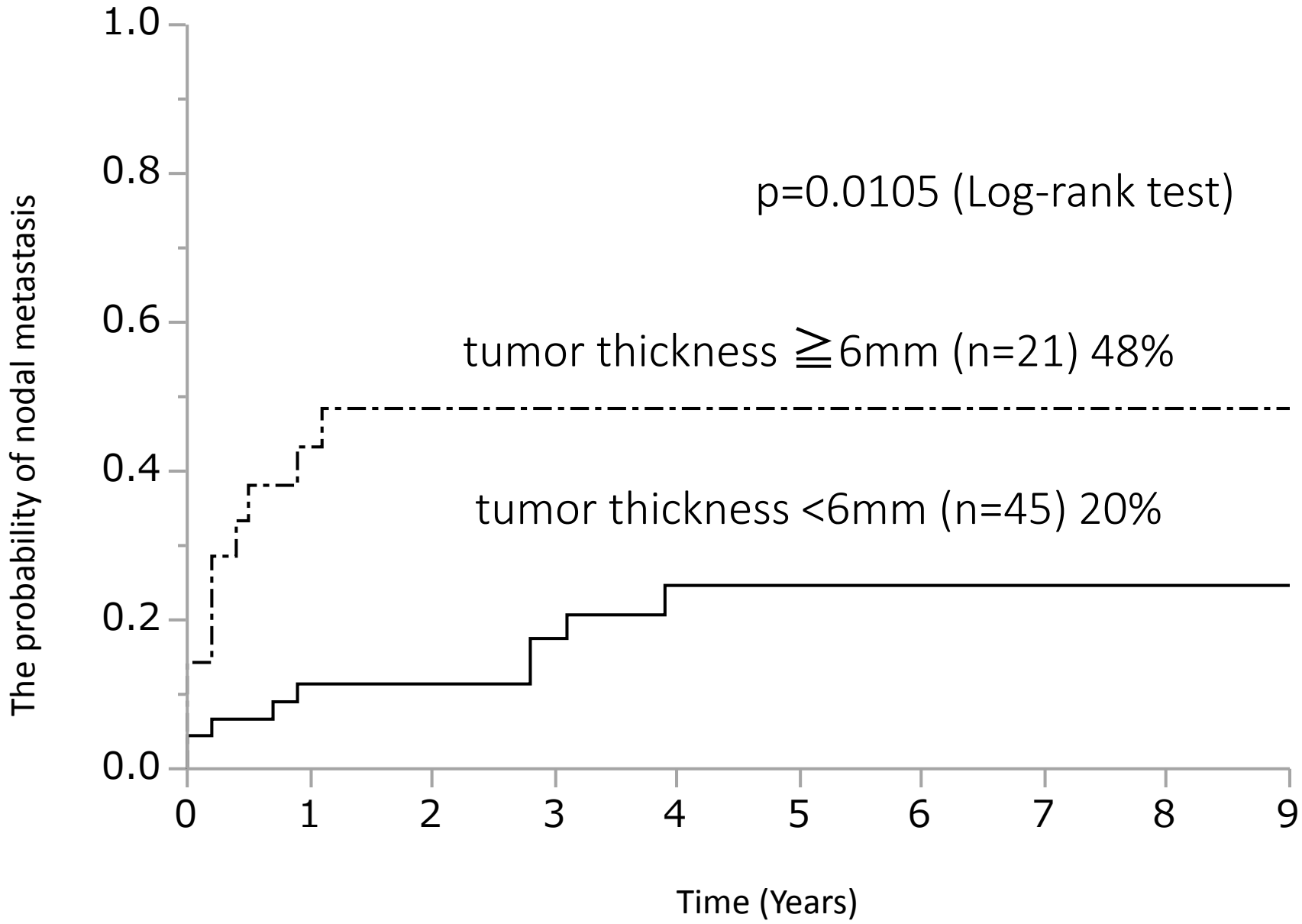
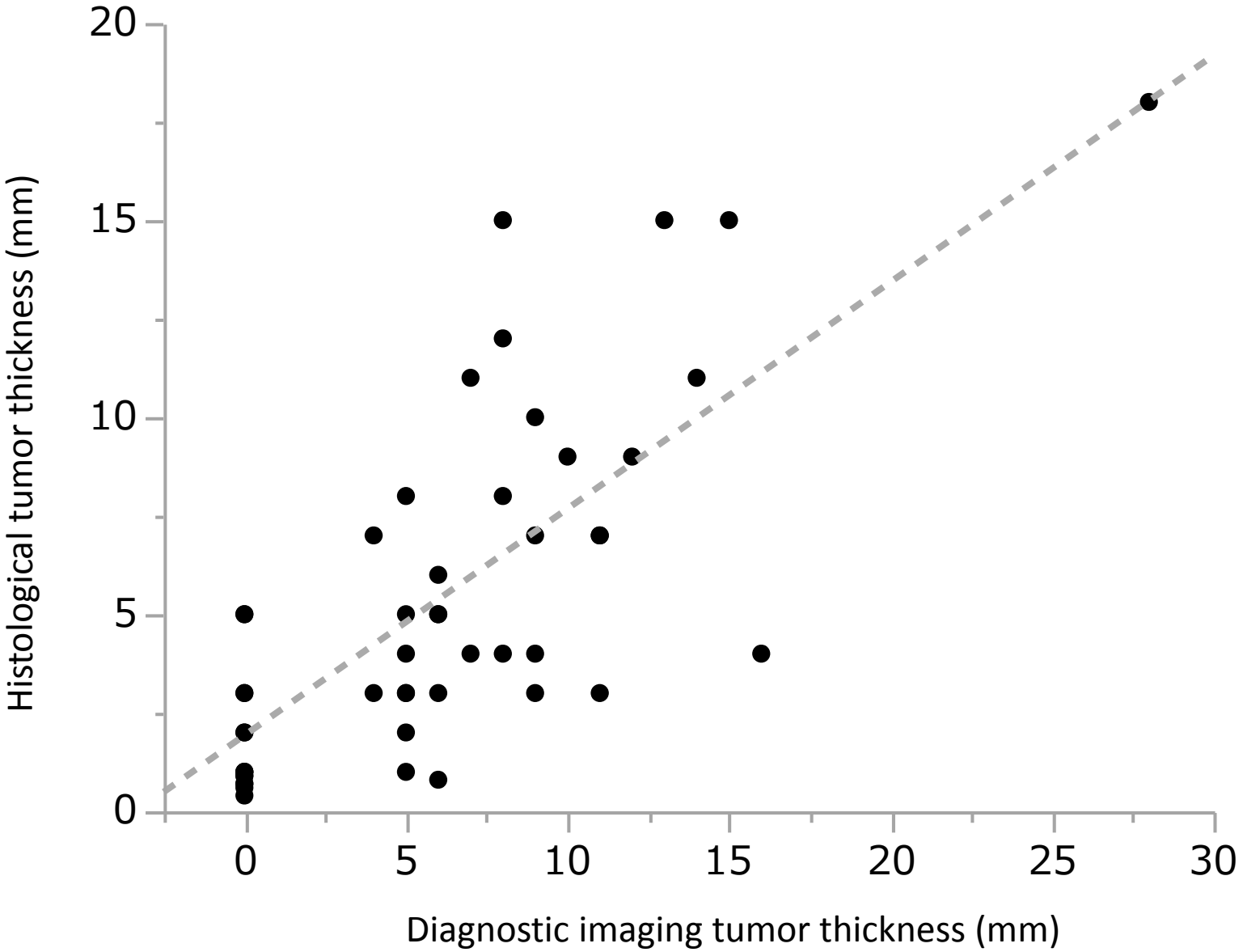

1.0
0.8
0.6
0.4
0.2
0.0
The probability of nodal metastasis
p=0.0105 (Log-rank test)
tumor thickness ≧6mm (n=21) 48%
tumor thickness <6mm (n=45) 20%
0
1
2
3
4
5
6
7
8
9
Time (Years)

Figure 7


Histological tumor thickness (mm)
20
15
10
5
0
0
5
10
15
20
25
30
Diagnostic imaging tumor thickness (mm)