

ORIGINAL ARTICLE

Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer

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ABSTRACT

BACKGROUND

Whether patients with early-stage oral cancers should be treated with elective neck dissection at the time of the primary surgery or with therapeutic neck dissection after nodal relapse has been a matter of debate.

METHODS

In this prospective, randomized, controlled trial, we evaluated the effect on survival of elective node dissection (ipsilateral neck dissection at the time of the primary surgery) versus therapeutic node dissection (watchful waiting followed by neck dissection for nodal relapse) in patients with lateralized stage T1 or T2 oral squamous-cell carcinomas. Primary and secondary end points were overall survival and disease-free survival, respectively.

RESULTS

Between 2004 and 2014, a total of 596 patients were enrolled. As prespecified by the data and safety monitoring committee, this report summarizes results for the first 500 patients (245 in the elective-surgery group and 255 in the therapeutic-surgery group), with a median follow-up of 39 months. There were 81 recurrences and 50 deaths in the elective-surgery group and 146 recurrences and 79 deaths in the therapeutic-surgery group. At 3 years, elective node dissection resulted in an improved rate of overall survival (80.0%; 95% confidence interval [CI], 74.1 to 85.8), as compared with therapeutic dissection (67.5%; 95% CI, 61.0 to 73.9), for a hazard ratio for death of 0.64 in the elective-surgery group (95% CI, 0.45 to 0.92; $P=0.01$ by the log-rank test). At that time, patients in the elective-surgery group also had a higher rate of disease-free survival than those in the therapeutic-surgery group (69.5% vs. 45.9%, $P<0.001$). Elective node dissection was superior in most subgroups without significant interactions. Rates of adverse events were 6.6% and 3.6% in the elective-surgery group and the therapeutic-surgery group, respectively.

CONCLUSIONS

Among patients with early-stage oral squamous-cell cancer, elective neck dissection resulted in higher rates of overall and disease-free survival than did therapeutic neck dissection. (Funded by the Tata Memorial Centre; ClinicalTrials.gov number, NCT00193765.)

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THE TREATMENT OF PATIENTS WITH EARLY-stage, clinically node-negative oral squamous-cell cancer has been a contentious issue spanning five decades. Such patients are usually treated with oral surgical excision of the primary tumor. Surgical options for addressing the neck include elective neck dissection at the time of the excision of the primary tumor or watchful waiting with therapeutic neck dissection for nodal relapse. Proponents of elective neck dissection cite decreased relapse rates and better survival rates.¹⁻⁷ However, others consider the evidence not to be definitive.^{8,9}

Data from prospective trials have also produced conflicting evidence.¹⁰⁻¹³ The watchful-waiting approach has the potential advantage of avoiding an additional surgical procedure in up to 70% of patients who eventually are found to be node-negative on histopathological analysis. In addition, neck dissection is associated with increased costs and complications. Moreover, nodal metastases could be detected at an early stage during follow-up with the use of ultrasonography without compromising outcomes.^{13,14} These considerations have led to variability in global practices.^{15,16}

This study was designed to address two issues. First, in patients with early-stage, clinically node-negative oral cancer, is there a survival difference between elective neck dissection and therapeutic neck dissection? Second, in the approach to such patients, does ultrasonography have a role in early detection of nodal metastases during follow-up?

Enrollment in this trial was stopped in June 2014 as recommended by the data and safety monitoring committee on the basis of evidence of the superiority of elective neck dissection. This report presents the findings with respect to the primary objective comparing elective versus therapeutic neck dissection in the first 500 patients who completed at least 9 months of follow-up.

METHODS

STUDY OVERSIGHT

The study was designed by academic investigators belonging to the Head and Neck Disease Management Group of the Tata Memorial Centre. Data were collected by the study team and analyzed in collaboration with all the authors, who vouch for the accuracy and completeness of data and analysis and adherence to the protocol. The

first author prepared the initial draft of the manuscript. All authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. This single-center trial was initiated after approval from the institutional ethics committee and was monitored by the institutional data and safety monitoring committee. The study protocol and amendments are available with the full text of this article at NEJM.org.

STUDY PATIENTS

The key eligibility criteria in patients between the ages of 18 and 75 years were histopathologically proven, invasive squamous-cell carcinoma of the oral cavity (tongue, floor of mouth, or buccal mucosa) that met the staging criteria of the Union for International Cancer Control tumor stage T1 (measuring ≤ 2 cm) or T2 (measuring >2 cm but <4 cm) that was lateralized to one side of the midline. In addition, all patients had received no previous treatment, were amenable to undergoing oral excision, and had no history of head and neck cancer. Exclusion criteria were previous surgery in the head and neck region, upper alveolar or palatal lesions, large heterogeneous leukoplasias, or diffuse oral submucous fibrosis.

TRIAL DESIGN

Patients were randomly assigned to undergo either elective or therapeutic neck dissection in a 1:1 ratio with the use of a prepared computerized block design. Patients were stratified according to tumor site (tongue, floor of mouth, or buccal mucosa), tumor stage (T1 or T2), sex, and findings on neck ultrasonography (indeterminate or suspicious vs. normal) before randomization. During the follow-up period, patients were randomly assigned to receive either physical (clinical) examination or physical examination plus ultrasonography of the neck at protocol-defined timepoints.

STUDY PROCEDURES

Surgery

We evaluated patients for primary tumor and lymph-node involvement using physical examination and ultrasonography of the neck. All patients underwent oral excision of the primary tumor with adequate margins (i.e., ≥ 5 mm). Patients in the elective-surgery group underwent an ipsilateral selective neck dissection with clearance of the submandibular (level I), upper jugular (level II), and midjugular (level III) nodes. In patients

with metastatic nodal disease that was discovered during surgery (operative findings or frozen section), a modified neck dissection was performed with nodal clearance extended to include the lower jugular (level IV) and posterior triangle (level V) nodes. Patients in the therapeutic-surgery group underwent the same surgical procedure for the primary tumor and were then monitored, with modified neck dissection (levels I to V) only at the time of nodal relapse.

Radiotherapy

When indicated, radiotherapy was used as an adjuvant treatment in the two study groups. (Details are provided in the Supplementary Appendix, available at NEJM.org.) All patients who had positive nodes, a primary-tumor depth of invasion of 10 mm or more, or a positive resection margin received adjuvant radiation. In patients with node-negative disease with a depth of invasion less than 10 mm, the decision to administer adjuvant radiation was individualized on the basis of the presence or absence of high-grade or perineural invasion or lymphovascular embolization. When two of these factors were present, adjuvant radiation was administered; in the presence of only one factor, the decision with respect to adjuvant radiation was made by the Head and Neck Disease Management Group.

Ultrasonography

Ultrasonography with the use of linear array transducers with a frequency ranging from 5 to 11 Mhz was performed in all patients before randomization and at each follow-up visit in patients who underwent secondary randomization to receive physical examination plus ultrasonography. To ensure uniformity, this procedure was supervised by the same group of radiologists throughout the study.

Histopathological Analysis

Histopathological findings were recorded in a prespecified synoptic reporting system. The details with respect to histopathological examination of the primary tumor and lymph nodes are provided in the Supplementary Appendix.

Follow-up

Patients were followed once every 4 weeks for first 6 months. After that, they were followed every 6 weeks for the next 6 months, every 8 weeks for next 12 months, and every 12 weeks thereafter.

STUDY OUTCOMES

The primary end point was overall survival, which was defined as the interval between the date of randomization and the date of death from any cause. The secondary end point was disease-free survival, which was defined as the interval between the date of randomization and the date of the first documented evidence of relapse at any site (local, regional, metastatic, or second primary) or death from any cause, whichever came first. The development of first nodal disease after the excision of the primary tumor in the therapeutic-surgery group was recorded as nodal relapse. Regional recurrence was defined as any recurrence in the neck in the elective-surgery group.

STATISTICAL ANALYSIS

The study was originally planned on the basis of a 5-year rate of overall survival of 60% in the therapeutic-surgery group, with an absolute increase in the rate of survival of 10 percentage points in the elective-surgery group at an alpha level of 0.05 and a statistical power of 80%. The calculated sample size was 710. This calculation accounted for a planned interim analysis after the occurrence of 250 deaths with an alpha level of less than 0.001 in favor of elective neck dissection as the predefined stopping boundary. An unplanned interim analysis (after the analysis of 248 patients and the occurrence of 43 deaths) was performed in 2011 after publication of a meta-analysis¹⁷ suggesting a benefit for elective neck dissection. However, the trial was continued, since the results did not meet the prespecified stopping criteria.

In June 2014, the data and safety monitoring committee requested another interim analysis on the basis of the observed difference in the rates of death in the two study groups. After the occurrence of 129 events, we performed an analysis involving the first 500 patients who underwent randomization. On the basis of a two-sided assumption, the O'Brien–Fleming spending function splits the alpha between the first analysis (performed in 2011, with a nominal alpha of 0.005), the second (current) analysis (with a nominal alpha of 0.027), and the final analysis (with a nominal alpha of 0.039), with upper test boundaries of 2.7898, 2.2029, and 2.0575, respectively. All P values and confidence intervals presented in this report are two-sided.

The primary and secondary end points were assessed in the intention-to-treat population and

tested by means of two-sided log-rank tests. We used the Kaplan–Meier method to estimate overall and disease-free survival. Analysis of overall and disease-free survival was performed in subgroups that were defined according to stratification factors with the use of univariate Cox analysis. In addition, we performed post hoc subgroup analyses on the basis of histological factors that were known to have an effect on survival.^{18,19} These factors included the grade of tumor differentiation (well or moderate vs. poor), the presence or absence of lymphovascular embolization or perineural invasion (as one variable), resection-margin status, and depth of invasion of the primary tumor. A Cox proportional-hazards model was used to perform multivariate analysis of various factors affecting overall and disease-

free survival, including the study intervention. All analyses were performed with the use of SPSS Statistics for Windows software, version 20.0 (IBM).

RESULTS

PATIENTS

From January 2004 through June 2014, we screened 1281 patients; 596 patients subsequently underwent randomization. The present analysis reports the findings in the first 500 patients (245 in the elective-surgery group and 255 in the therapeutic-surgery group) who had completed at least 9 months of follow-up at the data cutoff in June 2014 (Fig. 1). The median follow-up in this population was 39 months (interquartile range,

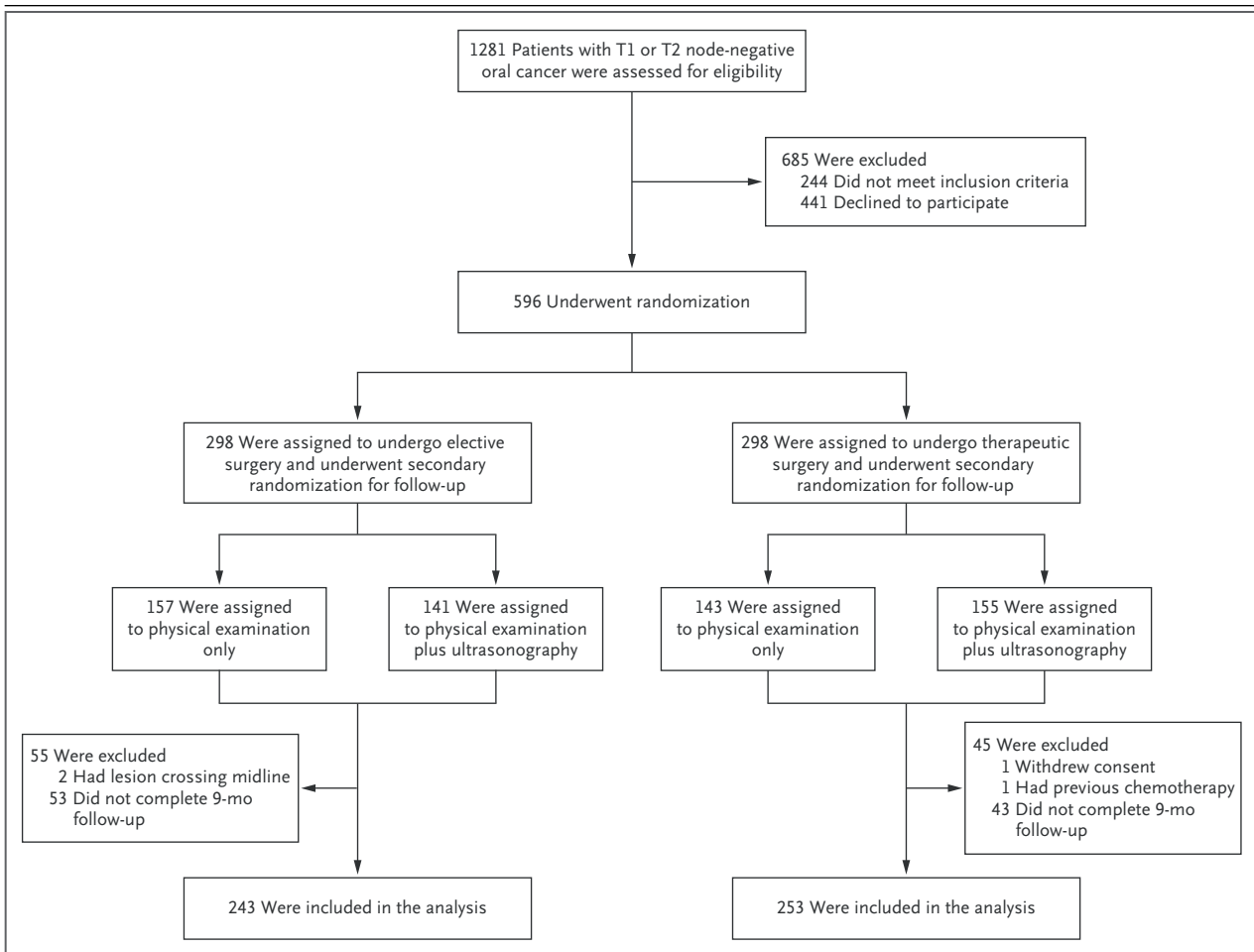


Figure 1. Study Enrollment.

Shown is the design of the study, including randomization of patients to undergo either elective surgery or therapeutic surgery and secondary randomization to either physical examination alone or physical examination plus ultrasonography during follow-up.

16 to 76) among surviving patients. The numbers of patients who were lost to follow-up were similar in the two groups (25 of 243 patients [10.3%] in elective-surgery group and 22 of 253 patients [8.7%] in the therapeutic-surgery group). The two study groups were well balanced with respect to baseline characteristics (Table 1, and Table S1 in the Supplementary Appendix).

The tongue was the most common site for primary tumor, and the majority of such tumors were moderately differentiated. A slightly higher percentage of patients received follow-up by means of both physical examination and ultrasonography in the therapeutic-surgery group than in the elective-surgery group. In the elective-surgery group, 174 patients underwent selective neck dissection, whereas 60 underwent modified neck dissection. Six patients did not comply with their assigned surgical treatment in our institution but underwent primary surgery elsewhere (5 patients in the elective-surgery group and 1 patient in the therapeutic-surgery group), and 8 patients did not undergo any surgery owing to nonadherence (5 in the elective-surgery group and 3 in the therapeutic-surgery group).

OVERALL SURVIVAL

There were 50 deaths (20.6%) in the elective-surgery group and 79 (31.2%) in the therapeutic-surgery group. At 3 years, the corresponding overall survival rates were 80.0% (95% confidence interval [CI], 74.1 to 85.8) and 67.5% (95% CI, 61.0 to 73.9), respectively (unadjusted hazard ratio for death in the elective-surgery group, 0.64; 95% CI, 0.45 to 0.92; $P=0.01$) (Fig. 2A). The rate of overall survival was also significantly higher in the elective-surgery group after adjustment for covariates (adjusted hazard ratio, 0.63; 95% CI, 0.44 to 0.90) (Tables S2A and S2B in the Supplementary Appendix).

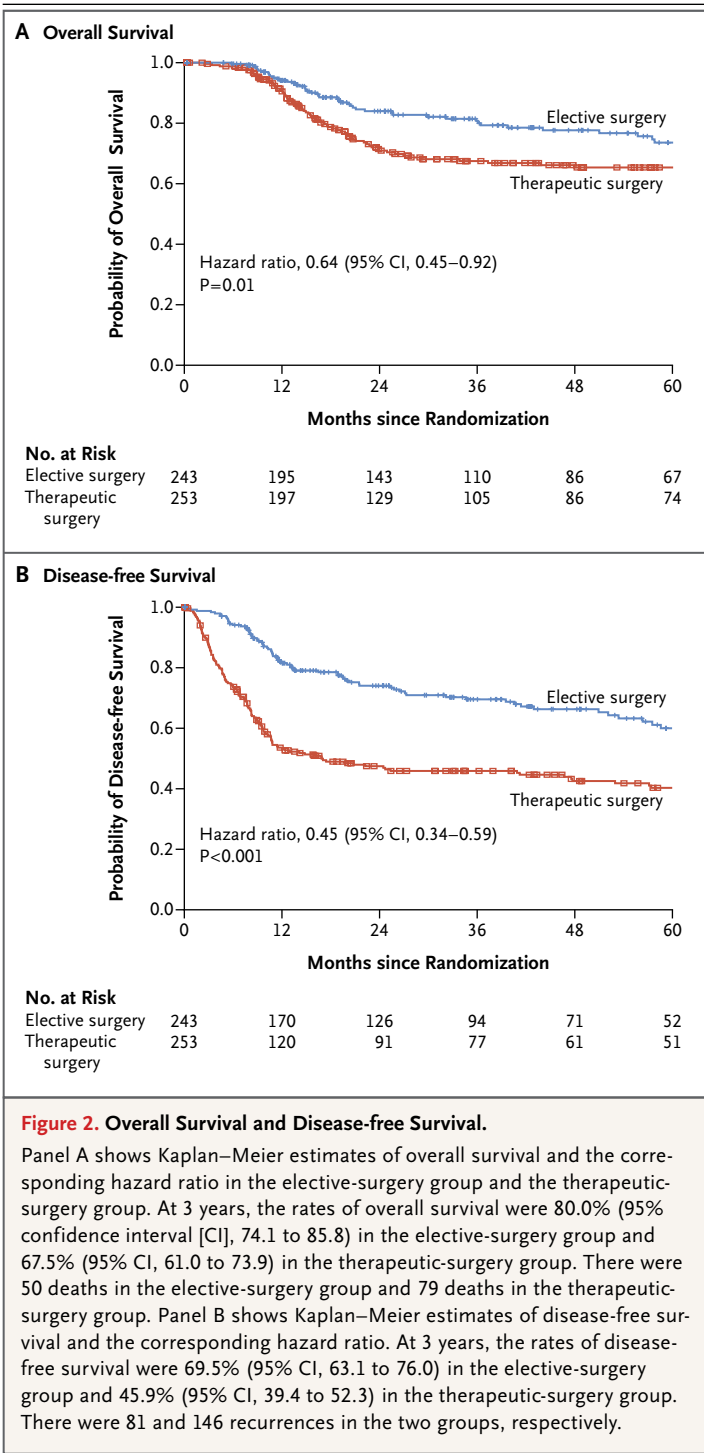
DISEASE-FREE SURVIVAL

There were 81 recurrences (33.3%) in the elective-surgery group and 146 (57.7%) in the therapeutic-surgery group. At 3 years, the corresponding rates of disease-free survival were 69.5% (95% CI, 63.1 to 76.0) and 45.9% (95% CI, 39.4 to 52.3%), respectively (unadjusted hazard ratio, 0.45; 95% CI, 0.34 to 0.59; $P<0.001$) (Fig. 2B). The rate of disease-free survival was also significantly higher in the elective-surgery group

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Elective-Surgery Group (N=243)	Therapeutic-Surgery Group (N=253)	All Patients (N=496)
	<i>number (percent)</i>		
Mean age (range) — yr	48 (21–75)	48 (20–75)	48 (20–75)
Sex			
Male	187 (77.0)	187 (73.9)	374 (75.4)
Female	56 (23.0)	66 (26.1)	122 (24.6)
Site of primary tumor			
Tongue	207 (85.2)	216 (85.4)	423 (85.3)
Buccal mucosa	33 (13.6)	35 (13.8)	68 (13.7)
Floor of mouth	3 (1.2)	2 (0.8)	5 (1.0)
Tumor stage			
T1	105 (43.2)	114 (45.1)	219 (44.2)
T2	138 (56.8)	139 (54.9)	277 (55.8)
Baseline ultrasonography			
Normal	222 (91.4)	234 (92.5)	456 (91.9)
Indeterminate	19 (7.8)	17 (6.7)	36 (7.3)
Suspicious	2 (0.8)	2 (0.8)	4 (0.8)

* There were no significant differences between the two groups. Additional information regarding baseline characteristics is provided in Table S1 in the Supplementary Appendix.



after adjustment for covariates (adjusted hazard ratio, 0.44; 95% CI, 0.33 to 0.57) (Tables S3A and S3B in the Supplementary Appendix). Of the 114 patients with cervical-lymph-node relapse in the therapeutic-surgery group, 60 (52.6%) died of disease progression.

SUBGROUP ANALYSES

The overall survival benefit of elective neck dissection was seen across prespecified subgroups, as defined according to stratification factors and other factors known to affect survival (Fig. 3). Post hoc analysis according to the depth of invasion of the primary tumor was suggestive of a lack of benefit of elective neck dissection in the 71 patients with a tumor depth of invasion measuring 3 mm or less, but the test of interaction was not significant.

FACTORS AFFECTING SURVIVAL

Elective node dissection continued to have a significant effect on rates of overall and disease-free survival after adjustment for covariates, including stratification factors along with tumor grade, the presence or absence of lymphovascular embolization or perineural invasion, resection-margin status, and depth of tumor invasion. (The univariate and multivariate analyses of factors affecting overall survival are provided in Tables S2A and S2B, and analyses of factors affecting disease-free survival are provided in Tables S3A and S3B in the Supplementary Appendix.) In addition, tumor grade, presence or absence of lymphovascular embolization or perineural invasion, and depth of invasion were also significantly associated with overall survival.

PATTERNS OF RECURRENCE

The pattern of disease recurrence in the two study groups is shown in Table 2. The majority of first events (114 events in 146 patients [78.1%]) were nodal relapses in the therapeutic-surgery group. Patients with nodal relapse presented with a more advanced nodal stage ($P=0.005$) and a higher incidence of extracapsular spread ($P<0.001$) (Table S4 in the Supplementary Appendix). Among patients in the elective-surgery group, the majority of first events (42 events [51.9%]) were non-nodal recurrences (local or distant metastasis or second primary tumors).

We used a logistic-regression model to evaluate factors affecting lymph-node involvement on pathological analysis in the elective-surgery group, with tumor site, pathological tumor size, tumor grade, the presence or absence of lymphovascular embolization or perineural invasion, and depth of invasion (continuous variable) as covariates. There were 72 patients (29.6%; 95% CI, 23.9 to 35.3) who had positive nodes on pathological analysis. The depth of invasion of the primary

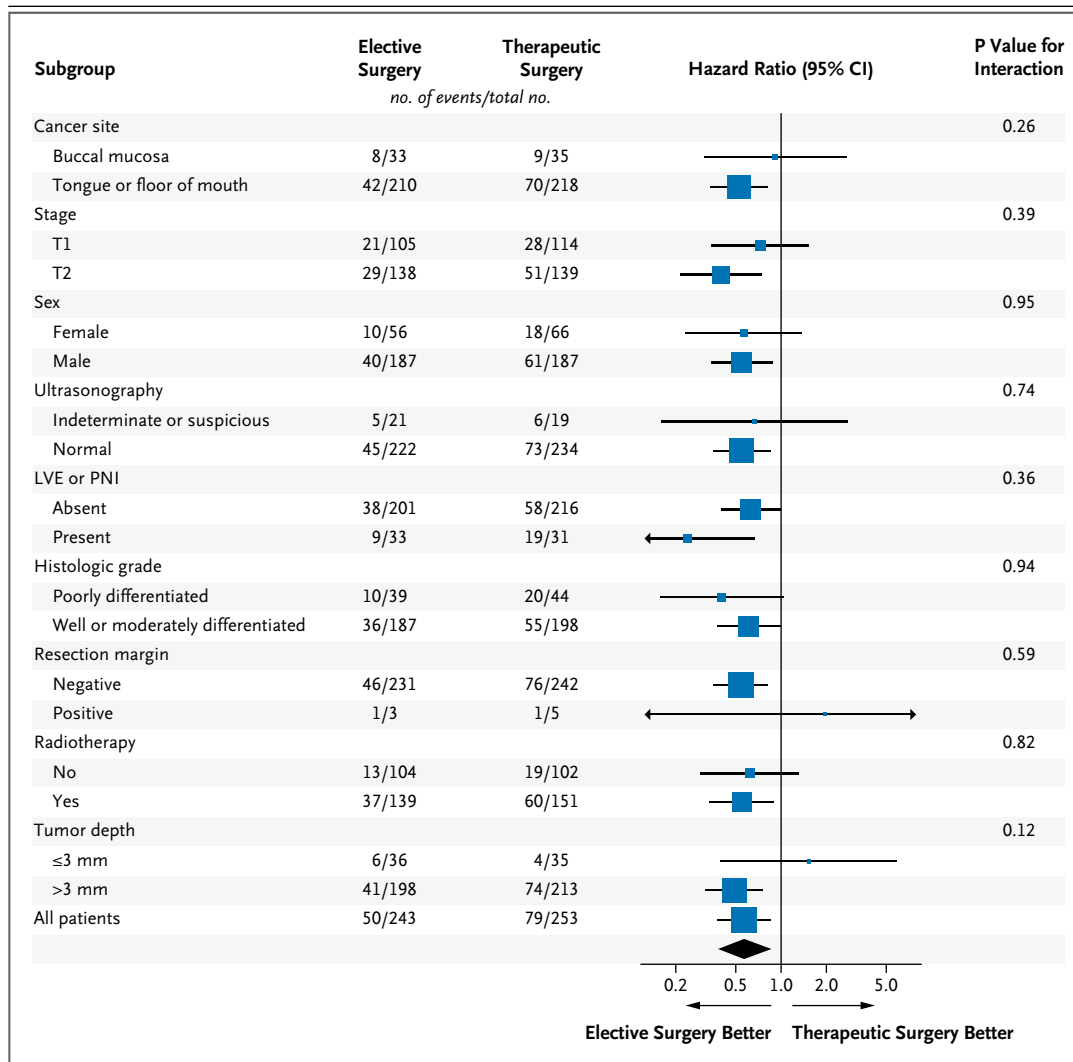


Figure 3. Overall Survival, According to Subgroup.

The subgroups were determined according to prespecified stratification factors and known prognostic factors. The size of the squares corresponds to the number of patients with an event. The diamond incorporates the point estimate and the 95% confidence interval of the overall effect. LVE denotes lymphovascular embolization, and PNI perineural invasion.

tumor was the only factor that was significantly associated with node positivity. A marked increase in cumulative lymph-node positivity was observed with increasing depth of invasion from 3 mm (5.6%) to 4 mm (16.9%).

ADVERSE EVENTS

Adverse events were reported in 6.6% of patients in the elective-surgery group and in 3.6% of those in the therapeutic-surgery group. A list of the major adverse events is provided in Table S5 in the Supplementary Appendix.

DISCUSSION

The results of our trial show the benefit of elective neck dissection at the time of primary surgery, as compared with watchful waiting followed by therapeutic neck dissection for nodal relapse, in patients with early-stage, clinically node-negative oral squamous-cell carcinoma. The results show an absolute overall survival benefit of 12.5 percentage points and a disease-free survival benefit of 23.6 percentage points. This means that eight patients would need to be

Table 2. Pattern of Recurrence.

Recurrence	Elective-Surgery Group (N=81)	Therapeutic-Surgery Group (N=146)
	<i>number (percent)</i>	
Nodal*	25 (30.9)	108 (74.0)
Local	23 (28.4)	7 (4.8)
Distant metastasis	3 (3.7)	3 (2.1)
Combination of above†	4 (4.9)	8 (5.5)
Second primary tumor	16 (19.8)	11 (7.5)
Not known	10 (12.3)	9 (6.2)

* In the elective-surgery group, nodal recurrence was defined as any recurrence in the neck. In the therapeutic-surgery group, nodal recurrence was defined as the development of first nodal disease after the excision of the primary tumor.

† Four patients in elective-surgery group and 6 patients in the therapeutic-surgery group had cervical lymph-node metastasis in combination with recurrence at a local or distant site.

treated with elective neck dissection to prevent one death, and four patients would need to be treated to prevent one relapse. A higher percentage of patients in the elective-surgery group received adjuvant radiotherapy on the basis of nodal indications, and the contribution of this factor to the improved rate of overall survival cannot be excluded. However, our trial was not designed to answer this question.

As expected, our results suggest that cervical lymph nodes remain the most important site of relapse in patients in whom neck dissection is not performed at the time of primary surgery. The adverse outcome associated with omission of elective neck dissection can at least partly be explained by the fact that patients with nodal relapse present with a more advanced nodal stage and higher incidence of extracapsular spread. This conclusion is also suggested by the fact that overall survival was significantly better in the node-positive patients in the elective-surgery group than in those with nodal relapse in the therapeutic-surgery group (Fig. S1 in the Supplementary Appendix). This advantage was noted despite the fact that our protocol mandated close and meticulous follow-up. Therefore, it is likely that in actual clinical practice, the rate of salvage of cervical-lymph-node relapse in patients who have not undergone elective neck dissection

would be even lower and the corresponding survival benefit of this procedure even higher.

In a meta-analysis of four prospective, randomized trials comparing elective and therapeutic neck dissection,¹⁷ there was a significant reduction in the disease-specific rate of death in favor of elective neck dissection. However, because of limitations of the meta-analysis, there continued to be a state of clinical equipoise. We have highlighted these aspects previously.²⁰

Of interest is the difference in the incidence of nodal relapse (114 of 253 patients [45.1%]) in the therapeutic-surgery group as compared with the incidence of node positivity (72 of 243 patients [29.6%]) in the elective-surgery group (Table S4 in the Supplementary Appendix). The most plausible explanation for this disparity could be the method of histopathological examination that was used in our study. Undetected metastases were probably missed on routine pathological examination. The use of serial-step sectioning and cytokeratin immunohistochemical staining, which are known to increase sensitivity, might have identified these occult lymph-node metastases.²¹ This disparity could also be attributed to the natural progression of untreated occult nodal disease in the therapeutic-surgery group.

In our study, the benefit of elective neck dissection was observed across several subgroups of patients. There is a suggestion that patients with a minimal depth (≤ 3 mm) of invasion of the primary tumor may not benefit from elective neck dissection. However, the number of such patients was small (71 patients), and the test of interaction was not significant. Therefore, this result is hypothesis-generating at best. Moreover, the use of the depth of invasion as a criterion for neck dissection has limited applicability, since there is currently no validated method of estimating this measurement before or at the time of primary surgery, as compared with the well-established accuracy of measurement on histopathological analysis.

The large majority of patients (85.3%) in our trial had tongue cancers, so the results are most applicable to this primary site. It is worth pointing out that although buccal cancers form the predominant subsite of oral cancers in our region, the majority of patients with such tumors were not suitable for recruitment because the tumors were not amenable to oral excision.

Our study has some limitations. The distress-

ing long-term complication of neck dissection is shoulder dysfunction, which occurs in a substantial proportion of patients.^{22,23} This complication was not addressed in our study. In this context, future studies should evaluate the role of procedures such as sentinel-lymph-node biopsy and limited neck dissection in reducing shoulder complications while preserving the rate of disease control. Furthermore, the sensitivity of ultrasonography for detecting neck nodal disease was low, and a better method could have resulted in the identification of patients with occult metastases who could have been excluded from a watchful-waiting policy. Translational studies to identify favorable subgroups of patients, with a

low propensity for nodal involvement in whom elective neck dissection is unlikely to be meaningful, could be another avenue for research.

In conclusion, the results of our trial suggest that elective neck dissection at the time of resection of the primary tumor confers an overall survival benefit in patients with early-stage, clinically node-negative oral squamous-cell carcinoma.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Lydiatt DD, Robbins KT, Byers RM, Wolf PF. Treatment of stage I and II oral tongue cancer. *Head Neck* 1993;15:308-12.
2. Yuen AP, Wei WI, Wong YM, Tang KC. Elective neck dissection versus observation in the treatment of early oral tongue carcinoma. *Head Neck* 1997;19:583-8.
3. Haddadin KJ, Soutar DS, Oliver RJ, Webster MH, Robertson AG, MacDonald DG. Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. *Head Neck* 1999;21:517-25.
4. Keski-Säntti H, Atala T, Törnwall J, Koivunen P, Mäkitie A. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. *Oral Oncol* 2006;42:96-101.
5. Capote A, Escorial V, Muñoz-Guerra MF, Rodríguez-Campo FJ, Gamallo C, Naval L. Elective neck dissection in early-stage oral squamous cell carcinoma — does it influence recurrence and survival? *Head Neck* 2007;29:3-11.
6. Huang SF, Kang CJ, Lin CY, et al. Neck treatment of patients with early stage oral tongue cancer: comparison between observation, supraomohyoid dissection, and extended dissection. *Cancer* 2008;112:1066-75.
7. Huang SF, Chang JT, Liao CT, et al. The role of elective neck dissection in early stage buccal cancer. *Laryngoscope* 2015;125:128-33.
8. Kramer D, Durham JS, Jackson S, Brookes J. Management of the neck in N0 squamous cell carcinoma of the oral cavity. *J Otolaryngol* 2001;30:283-8.
9. D'Cruz AK, Siddachari RC, Walvekar RR, et al. Elective neck dissection for the management of the N0 neck in early cancer of the oral tongue: need for a randomized controlled trial. *Head Neck* 2009;31:618-24.
10. Vandembrouck C, Sancho-Garnier H, Chassagne D, Saravane D, Cachin Y, Micheau C. Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. *Cancer* 1980;46:386-90.
11. Fakhri AR, Rao RS, Borges AM, Patel AR. Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. *Am J Surg* 1989;158:309-13.
12. Kligerman J, Lima RA, Soares JR, et al. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. *Am J Surg* 1994;168:391-4.
13. Yuen AP, Ho CM, Chow TL, et al. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. *Head Neck* 2009;31:765-72.
14. van den Brekel MW, Castelijns JA, Reitsma LC, Leemans CR, van der Waal I, Snow GB. Outcome of observing the N0 neck using ultrasonographic-guided cytology for follow-up. *Arch Otolaryngol Head Neck Surg* 1999;125:153-6.
15. Werning JW, Heard D, Pagano C, Khuder S. Elective management of the clinically negative neck by otolaryngologists in patients with oral tongue cancer. *Arch Otolaryngol Head Neck Surg* 2003;129:83-8.
16. Dünne AA, Folz BJ, Kuropkat C, Werner JA. Extent of surgical intervention in case of N0 neck in head and neck cancer patients: an analysis of data collection of 39 hospitals. *Eur Arch Otorhinolaryngol* 2004;261:295-303.
17. Fasnula AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. *Oral Oncol* 2011;47:320-4.
18. Jones HB, Sykes A, Bayman N, et al. The impact of lymphovascular invasion on survival in oral carcinoma. *Oral Oncol* 2009;45:10-5.
19. Thiagarajan S, Nair S, Nair D, et al. Predictors of prognosis for squamous cell carcinoma of oral tongue. *J Surg Oncol* 2014;109:639-44.
20. D'Cruz AK, Dandekar MR. Elective versus therapeutic neck dissection in the clinically node negative neck in early oral cavity cancers: do we have the answer yet? *Oral Oncol* 2011;47:780-2.
21. Civantos FJ, Moffat FL, Goodwin WJ. Lymphatic mapping and sentinel lymphadenectomy for 106 head and neck lesions: contrasts between oral cavity and cutaneous malignancy. *Laryngoscope* 2006;112:Suppl 109:1-15.
22. Pinsolle V, Michelet V, Majoufre C, Caix P, Siberchicot F, Pinsolle J. Spinal accessory nerve and lymphatic neck dissection. *Rev Stomatol Chir Maxillofac* 1997;98:138-42. (In French.)
23. Bradley PJ, Ferlito A, Silver CE, et al. Neck treatment and shoulder morbidity: still a challenge. *Head Neck* 2011;33:1060-7.

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