ORIGINAL ARTICLE

Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer

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ABSTRACT

BACKGROUND

Lenvatinib, an oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor α, RET, and KIT, showed clinical activity in a phase 2 study involving patients with differentiated thyroid cancer that was refractory to radioiodine (iodine-131).

METHODS

In our phase 3, randomized, double-blind, multicenter study involving patients with progressive thyroid cancer that was refractory to iodine-131, we randomly assigned 261 patients to receive lenvatinib (at a daily dose of 24 mg per day in 28-day cycles) and 131 patients to receive placebo. At the time of disease progression, patients in the placebo group could receive open-label lenvatinib. The primary end point was progression-free survival. Secondary end points included the response rate, overall survival, and safety.

RESULTS

The median progression-free survival was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001). A progression-free survival benefit associated with lenvatinib was observed in all prespecified subgroups. The response rate was 64.8% in the lenvatinib group (4 complete responses and 165 partial responses) and 1.5% in the placebo group (P<0.001). The median overall survival was not reached in either group. Treatment-related adverse effects of any grade, which occurred in more than 40% of patients in the lenvatinib group, were hypertension (in 67.8% of the patients), diarrhea (in 59.4%), fatigue or asthenia (in 59.0%), decreased appetite (in 50.2%), decreased weight (in 46.4%), and nausea (in 41.0%). Discontinuations of the study drug because of adverse effects occurred in 37 patients who received lenvatinib (14.2%) and 3 patients who received placebo (2.3%). In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered to be drug-related.

CONCLUSIONS

Lenvatinib, as compared with placebo, was associated with significant improvements in progression-free survival and the response rate among patients with iodine-131–refractory thyroid cancer. Patients who received lenvatinib had more adverse effects. (Funded by Eisai; SELECT ClinicalTrials.gov number, NCT01321554.)

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The 10-year survival rate among patients with differentiated thyroid cancer that is refractory to radioiodine (iodine-131) therapy is 10% from the time of detection of metastasis.[1-3] Although treatment options have historically been limited, efforts have first targeted vascular endothelial growth factor (VEGF) and its receptor (VEGFR), since this signaling network has been associated with the aggressiveness and metastasis of thyroid cancer.[4-6] However, other molecular pathways of tumor growth and maintenance beyond VEGF-driven angiogenesis contribute to the pathogenesis of thyroid cancer, including BRAF, NRAS, HRAS, RET/PTC, fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR).[7-16] Because of the involvement of these multiple pathways, multitargeted tyrosine kinase inhibitors are being investigated for the treatment of thyroid cancer that is refractory to iodine-131.[17-22] Recently, sorafenib, a tyrosine kinase inhibitor that inhibits VEGFRs 1, 2, and 3, PDGFR β, Raf-1, RET, and BRAF, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of iodine-131–refractory thyroid cancer on the basis of results of a phase 3 trial showing a 5-month improvement in median progression-free survival.[17]

Lenvatinib is an oral, multitargeted tyrosine kinase inhibitor of the VEGFRs 1, 2, and 3, FGFRs 1 through 4, PDGFR α, RET, and KIT signaling networks.[23,24] On the basis of results observed in a phase 2 study involving patients with iodine-131–refractory thyroid cancer,[25] we conducted the phase 3 Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) to assess progression-free survival among patients with iodine-131–refractory thyroid cancer who received lenvatinib as compared with those who received placebo.

METHODS

PATIENTS

Patients were eligible for enrollment if they were 18 years of age or older and had measurable, pathologically confirmed differentiated thyroid cancer, evidence of iodine-131–refractory disease (according to at least one of the following criteria: at least one measurable lesion without iodine uptake on any iodine-131 scan, at least one measurable lesion that had progressed according to the Response Evaluation Criteria In Solid Tumors [RECIST], version 1.1, criteria within 12 months after iodine-131 therapy despite iodine-131 avidity at the time of treatment, or cumulative activity of iodine-131 that was >600 mCi), and independently reviewed radiologic evidence of progression within the previous 13 months. Eligible patients had received no prior therapy with a tyrosine kinase inhibitor or had received one prior treatment regimen with a tyrosine kinase inhibitor. Additional inclusion and exclusion criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY OVERSIGHT

All patients provided written informed consent, and the study protocol was approved by all relevant institutional review bodies. The study was conducted in accordance with the provisions of the Declaration of Helsinki and local laws. The study was funded by Eisai and designed in collaboration with the principal investigators. Data collection and management were performed by Pharmaceutical Product Development (a contract research organization), and independent radiologic review was performed by VirtualScopics. Eisai statisticians performed the statistical analyses. All parties vouch for the accuracy and completeness of the data and analyses and for adherence to the study protocol. The first author wrote the manuscript with assistance from professional medical writers funded by Eisai. The study protocol, including the statistical analysis plan, is available at NEJM.org.

STUDY DESIGN

In this phase 3, randomized, double-blind, placebo-controlled, multicenter study, we recruited patients across the Americas, Europe, Asia, and Australia from August 5, 2011, through October 4, 2012. Eligible patients were stratified according to age, geographic region, and receipt or nonreceipt of prior tyrosine kinase inhibitor treatment, and they were randomly assigned in a 2:1 ratio to receive oral lenvatinib (at a dose of 24 mg once daily) or placebo in 28-day cycles. Block randomization was performed centrally by means of an interactive voice-response and Web-response system.

Study drugs were administered by clinicians who remained unaware of the study-drug assignments until the occurrence of unacceptable toxic effects or disease progression as assessed by independent radiologic review. Dose interrup-

tions and incremental reductions in the dose (to 20 mg, 14 mg, or 10 mg per day) because of toxic effects were permitted (see the Supplementary Appendix). If independent radiologic review confirmed disease progression, the patients who were receiving placebo could elect to enter the open-label lenvatinib phase.

EFFICACY

The primary end point was progression-free survival, which was defined as the time from randomization to the first documentation of disease progression by independent radiologic review or to death, in the intention-to-treat population (all patients who underwent randomization). Secondary end points were the response rate (defined as the best objective response [complete or partial]) according to RECIST, version 1.1 (Table S1 in the Supplementary Appendix),[26] and overall survival, which was defined as the time from randomization until death from any cause. Exploratory efficacy assessments included the rate of disease control (defined as a complete or partial response or stable disease) and the rate of clinical benefit (defined as a complete or partial response or durable stable disease for ≥23 weeks). Progression-free survival and response-rate outcomes in the optional open-label lenvatinib phase were also assessed.

Tumor assessments, consisting of computed tomographic or magnetic resonance imaging of the neck, chest, abdomen, pelvis, and all other known sites of disease, were evaluated in a blinded fashion by a central imaging laboratory, according to RECIST, version 1.1, criteria, every 8 weeks in the randomization phase. Tumor assessments were performed every 12 weeks in the extension phase, but they were not independently reviewed. Data on patients who were lost to follow-up and on patients who were alive at the time of the primary analysis were censored on the latest date on which the patient was known to be alive.

SAFETY AND ADVERSE EFFECTS

Safety assessments were performed throughout the study and included recording of symptoms and vital signs, electrocardiography, echocardiography (including left ventricular ejection fraction), hematologic and biochemical laboratory testing, and urinalysis. Adverse effects were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[27] Specific management plans were required for hypertension and proteinuria (see the Supplementary Appendix).

BIOMARKER ANALYSES

Exploratory biomarker analyses were performed to investigate potential markers of lenvatinib efficacy. Available archival formalin-fixed, paraffin-embedded tissues were obtained and analyzed for *BRAF* and *RAS* mutation hotspots with the use of Ion Torrent Personal Genome Machine amplicon sequencing.

STATISTICAL ANALYSIS

The study was designed to have 90% power to detect a 75% improvement in progression-free survival with lenvatinib versus placebo (hazard ratio for progression or death, 0.57) at a two-sided alpha level of 0.01, assuming a median progression-free survival of 14 months in the lenvatinib group and 8 months in the placebo group. At least 214 progression events or deaths in 392 enrolled patients were required for the primary analysis of progression-free survival. The rates of progression-free and overall survival in the intention-to-treat population for the primary analysis were estimated and plotted with the use of the Kaplan–Meier method and compared with the use of the stratified log-rank test. The hazard ratio and 99% (and 95%) confidence intervals were estimated with the use of stratified Cox proportional-hazards regression. The rates of response, clinical benefit, and disease control were compared with the use of Cochran–Mantel–Haenszel tests at a two-sided alpha level of 0.05.

The analysis of progression-free survival was based on the FDA guidance for progression-free survival,[28] and prespecified sensitivity analyses for progression-free survival were performed. These analyses included investigator assessment and the treatment of all cases of progressive disease, deaths, crossovers, and the subsequent use of anticancer therapy as events. Subgroup analyses were performed according to age (≤65 years vs. >65 years), sex, geographic region (Europe, North America, or other), histologic findings (papillary, poorly differentiated, follicular, or Hürthle-cell thyroid cancer), thyrotropin level (≤0.5, >0.5 to 2.0, or >2.0 to 5.5 mIU per liter), and receipt or nonreceipt of one prior tyrosine kinase inhibitor treatment. The analysis of overall survival was reported both as unadjusted and as adjusted for a potential crossover bias with the use of the rank-preserving structural failure time (RPSFT) mod-

el (see the Supplementary Appendix).[29] Hazard ratios and 95% confidence intervals were estimated with the use of the bootstrap method, with the survival time corrected for crossover in the placebo group.

RESULTS

PATIENTS

Overall, 392 patients from 21 countries were randomly assigned to receive lenvatinib (261 patients) or placebo (131 patients) (Fig. 1). All the patients received treatment and were included in the efficacy and safety analyses. The baseline characteristics of the patients were similar in the two groups (Table 1). At the time of data cutoff (November 15, 2013), the median duration of follow-up was 17.1 months (95% confidence interval [CI], 16.0 to 17.6; interquartile range, 14.4 to 20.4) in the lenvatinib group and 17.4 months (95% CI, 15.9 to 19.0; interquartile range, 14.8 to 20.4) in the placebo group, and 130 patients were still continuing to receive blinded treatment (122 patients who were randomly assigned to lenvatinib [46.7%] and 8 patients who were randomly assigned to placebo [6.1%]). Among 114 eligible patients who received placebo and had tumor progression confirmed by independent review, 109 (95.6%) elected to receive open-label lenvatinib. Of the patients who were randomly assigned to lenvatinib, 41 (15.7%) subsequently received additional anticancer therapies after disease progression.

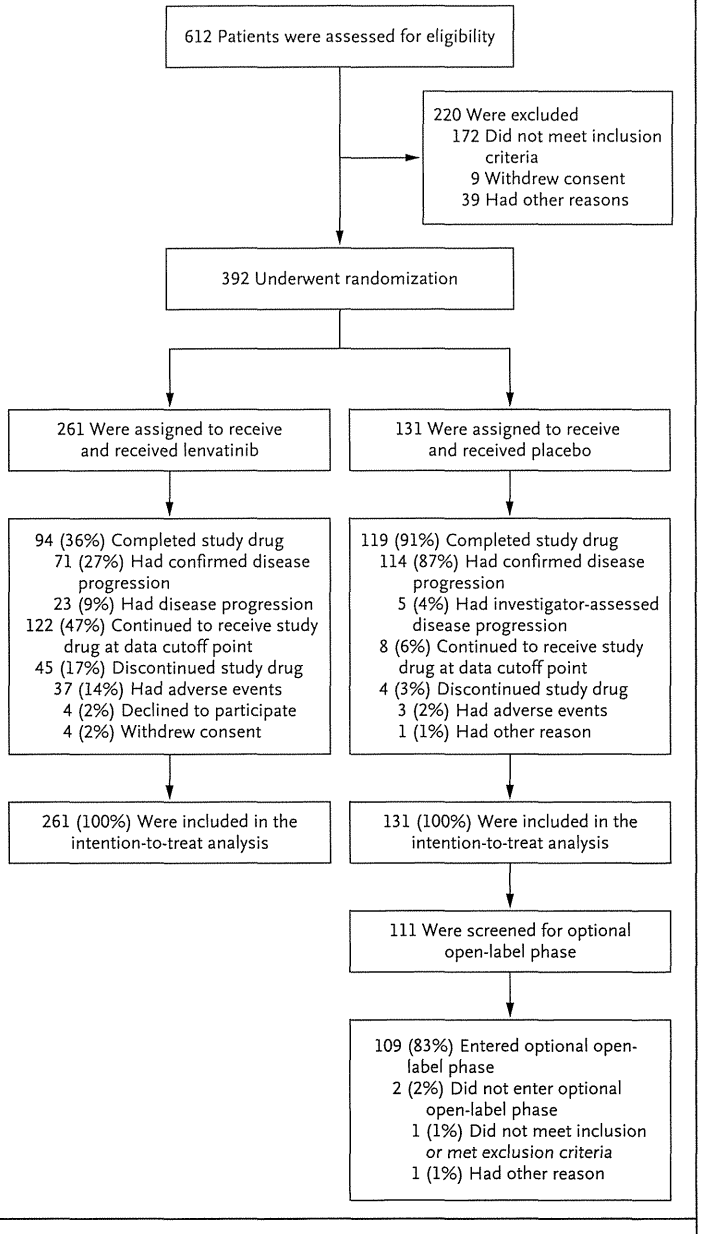

Figure 1. Enrollment, Randomization, and Treatment.

EFFICACY

At the time of the primary analysis of progression-free survival, there were 220 primary events: 202 patients had disease progression (93 [35.6%] in the lenvatinib group and 109 [83.2%] in the placebo group), and 18 patients had died before disease progression (14 in the lenvatinib group and 4 in the placebo group). The median progression-free survival was 18.3 months (95% CI, 15.1 to not estimable) with lenvatinib as compared with 3.6 months (95% CI, 2.2 to 3.7) with placebo (hazard ratio for progression or death, 0.21; 99% CI, 0.14 to 0.31; P<0.001) (Fig. 2). The 6-month progression-free survival rates were 77.5% in the lenvatinib group and 25.4% in the placebo group. Sensitivity analyses showed that a progression-free survival benefit associated with lenvatinib was maintained in all prespecified subgroups (i.e., subgroups defined according to age, sex, race or ethnic group, prior treatment or no prior treatment with a tyrosine kinase inhibitor, geographic region, histologic findings, and baseline thyrotropin levels) (Table 2, and Fig. S1 in the Supplementary Appendix). The median progression-free survival with lenvatinib was 18.7 months among patients who had not received previous treatment with a tyrosine kinase inhibitor and 15.1 months among those who had received one prior treatment regimen with a tyrosine kinase inhibitor (Fig. S1 and S2 in the Supplementary Appendix). A progression-free survival benefit

was observed in patients with thyroid cancer of all histologic types examined (papillary, poorly differentiated, follicular, and Hürthle-cell). Overall, 77 of 152 of patients (38 in the lenvatinib group and 39 in the placebo group) with baseline bone lesions (50.7%) had progressive disease at the time of data-collection cutoff. Progression of existing bone disease occurred in 9 of 38 patients in the lenvatinib group (23.7%) and in 23 of 39 patients in the placebo group (59.0%). Finally, the progression-free survival benefit associated with lenvatinib, as compared with placebo, was maintained regardless of the patient's *BRAF* or *RAS* mutation status (Fig. S1 in the Supplementary Appendix).

Lenvatinib was associated with significant improvement in the response rate (64.8% in the lenvatinib group vs. 1.5% in the placebo group; odds ratio, 28.87; 95% CI, 12.46 to 66.86; P<0.001) (Table 2, and Fig. S3 in the Supplementary Appendix). Complete responses occurred in 4 patients (1.5%) in the lenvatinib group as compared with no patients in the placebo group; partial responses occurred in 165 patients (63.2%) and 2 patients (1.5%), respectively; and durable stable disease for 23 weeks or longer occurred in 40 patients (15.3%) and 39 patients (29.8%), respectively. Progressive disease occurred in 18 patients (6.9%) in the lenvatinib group as compared with 52 patients (39.7%) in the placebo group. In all 4 patients who had a complete response, the response was maintained through the last time point assessed (range, 84 to 124 weeks). Lenvatinib was associated with a median time to objective response of 2 months (95% CI, 1.9 to 3.5). The difference in overall survival between the groups was not significant (hazard ratio for death, 0.73; 95% CI, 0.50 to 1.07; P=0.10 by a stratified log-rank test); this difference became larger when a potential crossover bias was considered (RPSFT model; hazard ratio, 0.62; 95% CI, 0.40 to 1.00; P=0.05 when calculated with the bootstrap method) (Fig. S4 in the Supplementary Appendix). The median progression-free survival among patients entering the open-label phase for whom data could be evaluated was 10.1 months (95% CI, 8.3 to not estimable), and the overall response rate was 52.3% (1 complete response and 56 partial responses).

Table 1. **Baseline Characteristics in the Intention-to-Treat Population.***

Variable	Lenvatinib (N=261)	Placebo (N=131)
Median age — yr	64	61
Male sex — no. (%)	125 (47.9)	75 (57.3)
Region — no. (%)		
Europe	131 (50.2)	64 (48.9)
North America	77 (29.5)	39 (29.8)
Other†	53 (20.3)	28 (21.4)
ECOG performance status — no. (%)‡		
0 or 1	248 (95.0)	129 (98.5)
2 or 3	13 (5.0)	2 (1.5)
One prior treatment regimen with a tyrosine kinase inhibitor — no. (%)§	66 (25.3)	27 (20.6)
Histologic subtype of differentiated thyroid cancer — no. (%)¶		
Papillary	132 (50.6)	68 (51.9)
Poorly differentiated	28 (10.7)	19 (14.5)
Follicular, not Hürthle cell	53 (20.3)	22 (16.8)
Hürthle cell	48 (18.4)	22 (16.8)
Metastatic lesions — no. (%)		
With bony metastases	104 (39.8)	48 (36.6)
With pulmonary metastases	226 (86.6)	124 (94.7)

* There were no significant differences between the groups in any of the characteristics listed in this table.
† Other regions include Brazil, Chile, Japan, South Korea, Russia, and Thailand.
‡ Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating increasing disability.
§ Further information is provided in Table S4 in the Supplementary Appendix.
¶ Histologic findings were determined from investigators' reports.

SAFETY AND SIDE-EFFECT PROFILE

The median duration of treatment was 13.8 months among patients who received lenvatinib and 3.9 months among patients who received placebo. The incidence of treatment-related adverse effects (of all grades) as assessed by the investigator was 97.3% in the lenvatinib group and 59.5% in the placebo group, and the incidence of treatment-related adverse effects of grade 3 or higher was 75.9% in the lenvatinib group and 9.9% in the placebo group (Table 3, and Table S2 in the Supplementary Appendix). Adverse effects of special interest that developed in the lenvatinib group during treatment were hypertension (any grade, 69.3%; grade ≥3, 42.9%), proteinuria (any grade, 32.2%; grade ≥3, 10.0%), arterial thromboembolic effects (any grade, 5.4%; grade ≥3, 2.7%), venous thromboembolic effects (any grade, 5.4%; grade ≥3, 3.8%), renal failure, including acute renal failure (any grade, 4.2%; grade ≥3, 1.9%), hepatic failure (grade ≥3, 0.4%), gastrointestinal fistula (any grade, 1.5%; grade ≥3,

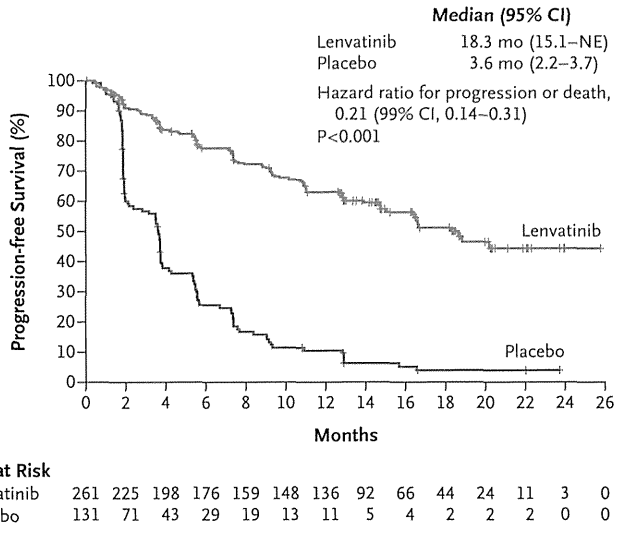

Figure 2. Kaplan–Meier Estimate of Progression-free Survival in the Intention-to-Treat Population.

Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent centralized radiologic review. Tumor responses were calculated as the maximum percentage change from baseline in the sum of the diameters of target lesions. CI denotes confidence interval, and NE not estimable.

0.8%), corrected QT prolongation (any grade, 8%; grade ≥3, 1.5%), and the posterior reversible encephalopathy syndrome (any grade, 0.4%; grade ≥3, 0). In patients who received lenvatinib, the median serum thyrotropin levels increased from baseline levels in cycle 1 and peaked by cycle 2. The post-baseline levels of serum thyrotropin increased to more than 0.5 mIU per liter in 158 patients in the lenvatinib group (61.5%).

A total of 118 deaths occurred before data cutoff: 71 in the lenvatinib group (27.2%) and 47 in the placebo group (35.9%) (P=0.08). The majority of these deaths were due to disease progression (53 [74.6%] and 35 [74.5%] in the lenvatinib and placebo groups, respectively); the remaining deaths were either not due to progressive disease or were due to an unknown cause. In 20 patients in the lenvatinib group (7.7%), adverse effects that developed during treatment were fatal (Table S3 in the Supplementary Appendix). Of these, 6 deaths (2.3%) were considered by the investigator to be treatment-related, including 1 case each of pulmonary embolism, hemorrhagic stroke, and general deterioration of physical health; 3 cases were reported as deaths or sudden deaths (not otherwise specified). In 6 patients in the placebo group (4.6%), adverse effects that occurred during the treatment period were fatal; none were considered to be treatment-related.

Adverse effects that developed during treatment and led to the discontinuation of treatment were reported in 37 patients who were receiving lenvatinib (14.2%) and in 3 patients who were receiving placebo (2.3%). The most frequent effects leading to dose discontinuation were asthenia and hypertension, each of which occurred in 1.1% of patients in the lenvatinib group. More patients in the lenvatinib group than in the placebo group had a dose interruption (82.4% vs. 18.3%) or reduction (67.8% vs. 4.6%), resulting in a mean lenvatinib dose of 17.2 mg per day. The first dose reduction occurred at a median of 3.0 months (95% CI, 2.7 to 3.7). The most common adverse effects developing during treatment that led to a dose interruption or reduction among patients receiving lenvatinib were diarrhea (22.6%), hypertension (19.9%), proteinuria (18.8%), and decreased appetite (18.0%). Four patients in the lenvatinib group (1.5%) required dose adjustments owing to hypocalcemia.

DISCUSSION

Among patients with progressive iodine-131–refractory differentiated thyroid cancer who received lenvatinib, the median progression-free survival was 14.7 months longer than it was among those who received placebo (hazard ratio for disease progression or death, 0.21; 99% CI, 0.14 to 0.31; P<0.001). This improvement is longer than that observed in other placebo-controlled clinical trials involving patients with this disease.[17,18,20-22] One distinguishing feature of lenvatinib that may underlie this observation is the inhibition of unique targets, including FGFRs.[10] The median progression-free survival in the placebo group in this study was shorter than the 8 months expected, indicating that these patients had aggressive thyroid cancer. The 8-month assumption was conservative and was made before results from similar trials were available. This study is unusual in that all patients had independently verified progressive disease at the time of enrollment. In addition, it is unlikely that investigator bias factored into the observed results in the placebo group, since progression also required confirmation by independent review. The

Table 2. **Efficacy Measures.***

Outcome	Lenvatinib (N=261)	Placebo (N=131)	Hazard Ratio†	Odds Ratio (95% CI)
Progression-free survival				
Primary analysis, IRR and ITT populations‡				
Median (95% CI) — mo	18.3 (15.1–NE)	3.6 (2.2–3.7)	0.21 (0.14–0.31)§	
Rate — % (95% CI)				
6 mo	77.5 (71.7–82.3)	25.4 (18.0–33.6)		
12 mo	63.0 (56.5–68.9)	10.5 (5.7–16.9)		
18 mo	51.1 (43.3–58.3)	3.8 (1.1–9.2)		
24 mo	44.3 (35.1–53.1)	NE		
Prespecified sensitivity analyses				
Investigator assessment, ITT population — mo			0.24 (0.16–0.35)§	
Median	16.6	3.7		
95% CI	14.8–NE	3.5–5.4		
IRR population — mo¶			0.22 (0.15–0.32)§	
Median	16.6	3.6		
95% CI	14.8–20.3	2.2–3.7		
Secondary efficacy end points				
Overall survival, RPSFT adjusted, ITT population			0.62 (0.40–1.00)‖	
Median (95% CI) — mo	NE (22.0–NE)	NE (14.3–NE)		
Rate, RPSFT adjusted — % (95% CI)				
6 mo	90.7 (86.4–93.7)	85.3 (78.0–90.4)		
12 mo	81.6 (76.2–85.8)	70.0 (57.1–79.7)		
18 mo	72.3 (65.7–77.9)	63.0 (44.3–76.9)		
24 mo	58.2 (46.0–68.6)	NE		
Response rate — no. (%)**	169 (64.8)	2 (1.5)		28.87 (12.46–66.86)§
Complete response	4 (1.5)	0		
Partial response	165 (63.2)	2 (1.5)		
Stable disease	60 (23.0)	71 (54.2)		
Durable stable disease ≥23 wk	40 (15.3)	39 (29.8)		
Progressive disease	18 (6.9)	52 (39.7)		
Could not be evaluated	14 (5.4)	6 (4.6)		
Exploratory efficacy end points				
Disease-control rate — no. (%)††	229 (87.7)	73 (55.7)		5.05 (2.98–8.54)§
Clinical-benefit rate — no. (%)§§	209 (80.1)	41 (31.3)		7.63 (4.55–12.79)§
Time to first objective response — mo				
Median	2.0	5.6		
95% CI	1.9–3.5	1.8–9.4		

* CI denotes confidence interval, IRR independent radiologic review, ITT intention-to-treat, NE not estimable, and RPSFT rank-preserving structural failure time.
† Corresponding confidence intervals were 99%, with the exception of the confidence interval for overall survival, which was 95%.
‡ The analysis involving the per-protocol population yielded identical results.
§ P<0.001 for the comparison between the two groups.
¶ This sensitivity analysis treated all cases of progressive disease, deaths, crossovers, and use of new anticancer therapies (even in patients who were not receiving a study drug) as events.
‖ P=0.05 when calculated with the use of the bootstrap method.
** Tumor responses were assessed with the use of Response Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent centralized radiologic review.
†† The disease-control rate was calculated as complete response plus partial response plus stable disease.
§§ The clinical-benefit rate was calculated as complete response plus partial response plus durable stable disease.

Table 3. Adverse Effects.

Effect	Lenvatinib (N=261)		Placebo (N=131)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any treatment-related adverse effect — no. of patients (%)	254 (97.3)	198 (75.9)	78 (59.5)	13 (9.9)
Adverse effect developing during treatment — no. of patients (%)				
Serious*				
Total	130 (49.8)		30 (22.9)	
Treatment-related	79 (30.3)		8 (6.1)	
Fatal				
Total†	20 (7.7)		6 (4.6)	
Treatment-related	6 (2.3)		0	
Treatment-related adverse effect of any grade in ≥10% of patients, of grade ≥3 in ≥2%, or both — %				
Hypertension	67.8	41.8	9.2	2.3
Diarrhea	59.4	8.0	8.4	0
Fatigue or asthenia	59.0	9.2	27.5	2.3
Decreased appetite	50.2	5.4	11.5	0
Decreased weight	46.4	9.6	9.2	0
Nausea	41.0	2.3	13.7	0.8
Stomatitis	35.6	4.2	3.8	0
Palmar–plantar erythrodysesthesia syndrome	31.8	3.4	0.8	0
Proteinuria	31.0	10.0	1.5	0
Vomiting	28.4	1.9	6.1	0
Headache	27.6	2.7	6.1	0
Dysphonia	24.1	1.1	3.1	0
Arthralgia	18.0	0	0.8	0
Dysgeusia	16.9	0	1.5	0
Rash	16.1	0.4	1.5	0
Constipation	14.6	0.4	8.4	0
Myalgia	14.6	1.5	2.3	0
Dry mouth	13.8	0.4	3.8	0
Upper abdominal pain	13.0	0	3.8	0
Abdominal pain	11.5	0.4	0.8	0.8
Peripheral edema	11.1	0.4	0	0
Alopecia	11.1	0	3.8	0
Dyspepsia	10.0	0	0	0
Oropharyngeal pain	10.0	0.4	0.8	0
Hypocalcemia	6.9	2.7	0	0
Pulmonary embolism	2.7	2.7	1.5	1.5

* A complete list of serious adverse effects is provided in Table S2 in the Supplementary Appendix.
† A complete list of fatal adverse effects that developed during treatment is provided in Table S3 in the Supplementary Appendix.

8.2-month difference in the median progression-free survival between patients who were initially randomly assigned to lenvatinib and those who crossed over to lenvatinib may be attributed in part to the necessary additional progression event in the latter group.

The progression-free survival benefit with lenvatinib was observed across all prespecified sub-

groups, including patients who had received one prior tyrosine kinase inhibitor treatment (Fig. S2 in the Supplementary Appendix). This efficacy after prior treatment with a tyrosine kinase inhibitor is a key clinical consideration given the likely increased use of these therapies in patients with iodine-131–refractory thyroid cancer. The proportion of patients in whom progression of existing bone metastases occurred was lower in the lenvatinib group than in the placebo group (23.7% vs. 59.0%), and this difference indicates that in this small subgroup of patients, lenvatinib is able to curtail these often-intractable metastases. The median overall survival was not reached; the majority of patients who received placebo crossed over to lenvatinib, and a nonsignificant prolongation in overall survival with lenvatinib was observed (adjusted hazard ratio, 0.62).

The proportion of patients who received lenvatinib and who had treatment-related adverse effects was 97.3%, and 75.9% had treatment-related adverse effects that were grade 3 or higher. Previous studies showed an increased risk of hypertension and proteinuria among patients who received lenvatinib; these findings are consistent with those among patients receiving other VEGF and VEGFR inhibitors.[30,31] Overall, 41.8% of the patients who received lenvatinib, as compared with 2.3% of those who received placebo, had treatment-related hypertension of grade 3 or higher. However, hypertension led to discontinuation of the drug in only 1.1% of the patients in the lenvatinib group and dose reduction or interruption in 19.9% of the patients in that group. Most adverse effects were managed with standard clinical interventions or dose modifications.[31,32] The rate of discontinuation of lenvatinib because of adverse effects that developed during treatment was 14.2%, the median duration of treatment was 13.8 months, and patients who received lenvatinib received a mean dose of 17.2 mg per day. The median time to the first dose reduction was 3.0 months, or 1 month after the median time to the first objective response (2.0 months), which was also the time of the first radiologic tumor assessment. There were more fatal adverse effects during treatment in the lenvatinib group than in the placebo group (7.7% vs. 4.6%), and 6 of 20 deaths in the lenvatinib group (2.3%) were considered to be treatment-related, including 1 case each of pulmonary embolism and hemorrhagic stroke. No specific pattern of fatal adverse effects in the lenvatinib group was observed. In patients who receive lenvatinib, serum thyrotropin levels should be measured on a regular basis, and the daily dose of levothyroxine should be increased accordingly if the level rises.

In this placebo-controlled analysis, a progression-free survival benefit associated with lenvatinib was maintained regardless of *BRAF* or *RAS* mutation status; neither mutational status appeared to predict a benefit with lenvatinib. Therefore, further investigation of biomarkers for lenvatinib efficacy is necessary. Limitations of this study include the possibility that crossovers from placebo to lenvatinib could have confounded the survival analysis, a limitation that we attempted to address with adjusted analyses, and a lack of information on the patients' quality of life.

In conclusion, this study showed that lenvatinib, as compared with placebo, was associated with significant prolongation of progression-free survival and an improved response rate (64.8% vs. 1.5%) among patients with iodine-131–refractory differentiated thyroid cancer. Toxic effects of therapy were considerable, and most toxic effects were managed with dose modification and medical therapy.

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APPENDIX

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Hearing Preservation after Lateral Temporal Bone Resection for Early-Stage External Auditory Canal Carcinoma

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Key Words
External auditory canal carcinoma · Hearing preservation · Early stage · Tympanoplasty · Reconstruction

Abstract
Objective: To evaluate postoperative hearing outcomes after lateral temporal bone resection (LTBR) with reconstruction of the external auditory canal (EAC) and conductive function for early-stage EAC carcinoma. ***Methods:*** We retrospectively examined patients diagnosed with early-stage EAC carcinoma treated with surgery alone between January 2006 and December 2012. Patients who had postoperative adjuvant chemotherapy and/or radiotherapy were excluded. Patients receiving LTBR in combination with tympanoplasty were divided into two groups based on the reconstruction of the EAC with and without (w/o) split-thickness skin grafts (STSGs). Audiological data included the preoperative hearing thresholds and the most recent postoperative hearing thresholds obtained at least 12 months after surgery. The hearing outcome was evaluated based on pure-tone audiograms using the Committee on Hearing and Equilibrium guidelines of the American Academy of Otolaryngology-Head and Neck Surgery for the evaluation of the results of treatment of conductive hearing loss. The postoperative quality of life (QOL) for patients was evaluated using the Glasgow Benefit Inventory (GBI). ***Results:*** All patients (n = 15) achieved disease-free survival without significant morbidity or mortality. When we compared the mean air-bone gaps after surgery, those in the STSG group (n = 8) were found to be significantly lower than those in the w/o STSG group (n = 7; $p < 0.001$). The success rate for postoperative hearing was 75.0% in the STSG group, which was significantly higher than that in the w/o STSG group ($p = 0.014$). All patients in the w/o STSG group showed stenosis and closure of the EAC at fewer than 10 months after surgery. In contrast, all patients in the STSG group showed preserved conformation of the new EAC for more than 12 months after surgery. When we compared the mean GBI score between the two groups of patients, the overall and general health scores in the STSG group were found to be significantly higher than those in the w/o STSG group ($p = 0.021$, $p = 0.001$). ***Conclusions:*** Reconstruction of the EAC using a rolled-up STSG technique in combination with tympanoplasty after LTBR is useful for hearing preservation and the observation of locoregional lesions after surgery, resulting in improved QOL for patients.

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Introduction

External auditory canal (EAC) carcinoma has been reported to be an aggressive tumor with a poor prognosis, especially in the advanced stage [Nakagawa et al., 2006; Yin et al., 2006; Zhang et al., 1999]. The complexity of the temporal bone anatomy, which includes major vessels, cranial nerves and intracranial structures, makes the surgical procedure for EAC carcinoma particularly challenging. However, early diagnosis and adequate management of early-stage EAC carcinoma can afford a good prognosis [Barrs, 2001; Pfreundner et al., 1999; Spector, 1991; Yin et al., 2006; Zhang et al., 1999]. Surgery is usually recommended for resectable EAC tumors, and complete resection is the best approach to improve the prognosis [Zhang et al., 2013].

Considering the good survival rates for early-stage EAC carcinoma, reconstruction of the EAC with tympanoplasty after tumor resection has been performed to preserve hearing ability and improve patient quality of life (QOL) [Hoshikawa et al., 2012; Iida et al., 2013; Koshima et al., 2004; Zhang et al., 2013]. However, conductive hearing loss may worsen after lateral temporal bone resection (LTBR) due to postoperative complications such as chronic infection, bone exposure, stenosis and closure of the EAC [Iida et al., 2013; Zhang et al., 2013]. To prevent these adverse events, several methods, such as the use of a local flap, free flap or skin graft, have been reported [Bell, 1988; Hoshikawa et al., 2012; Iida et al., 2013; Koshima et al., 2004]. Meanwhile, the details of postoperative hearing ability for patients with EAC carcinoma have not been well described in the literature.

In this retrospective study, we focused on the reconstruction of the EAC with tympanoplasty after LTBR for early-stage EAC carcinoma, with the aim of evaluating postoperative hearing outcome.

Materials and Methods

Patients

We performed a retrospective, single-institution review of patients with early-stage EAC carcinoma initially treated with surgery alone in the Department of Otolaryngology, Head and Neck Surgery, Hokkaido University Hospital between January 2006 and December 2012. Preoperative biopsy was performed to establish the diagnosis in all cases. Prior to treatment, all patients underwent a thorough history-taking, physical examination, routine blood tests, including full blood count and blood biochemistry, pure-tone audiometry, computed tomography (CT), magnetic resonance imaging (MRI) and/or [^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}FDG-PET/CT). We used the Pittsburgh staging system, which is based on preoperative clinical findings and imaging (CT, MRI, ^{18}FDG-PET/CT) [Moody et al., 2000]. For patients with stage I (T1N0) and stage II (T2N0) EAC carcinoma, LTBR without neck dissection was selected as the initial choice. The extent of the disease was confirmed by intraoperative and histologic findings. If histologic criteria revealed positive surgical margins, postoperative adjuvant chemotherapy and/or radiotherapy were performed. We excluded the patients receiving these additional treatments from this analysis. Patients treated with surgery in combination with tympanoplasty were divided into two groups based on the reconstruction of the EAC with and without (w/o) split-thickness skin grafts (STSGs). All patients were required to be cleared for treatment. After full discussion of the potential risks and benefits, informed consent was obtained from all patients. Patients who could not accept the use of skin from another area, such as the upper thigh, and rejected the reconstruction of the EAC using an STSG technique, underwent reconstruction by local-pedicled flaps only (w/o STSG group). This research adhered to the tenets of the Declaration of Helsinki and was approved by our Institutional Review Board.

Surgical Procedure

LTBR was conducted in a manner similar to the technique described by Hirsch and Chang [1997]. A circumferential incision was made around the concha and tragal cartilage, and a curved postauricular incision was made approximately 1 cm posterior to the postauricular sulcus. The superior rim of the incision extended for approximately 2 cm superiorly toward the temporal area. The inferior limit of the incision extended approximately 3 cm inferiorly toward the mastoid tip. The temporalis muscle was elevated from the periosteum using blunt dissection, exposing the periosteum of the squamous portion of the temporal bone. An anteriorly based temporalis muscle-pedicled flap of approximately 6 × 4 cm was constructed. An inferiorly based periosteal-pedicled flap was then constructed by sharply incising the postauricular subcutaneous tissue along the border of the posterior bony canal aperture. The incision was extended superiorly to the level of the temporalis muscle. The periosteum was the superior extension of this inferiorly based flap (fig. 1a). The next procedure was to perform a canal wall-up mastoidectomy with an extended facial recess approach. Once the facial recess was widely opened, access through the facial recess allowed for division of the incudostapedial joint and removal of the incus. Working through the inferior aspect of the extended facial recess, a cleft was developed between the jugular bulb and the tympanic annulus and extended anteriorly toward the region of the glenoid fossa. Similarly, the bone was removed anteriorly and superiorly along the tegmental plate to the superior attachment of the bony canal in the anterior epitympanum, and the specimen was removed by en bloc technique. When bony destruction, invasion to middle ear or skip lesions in the mastoid cells were revealed, intraoperative rapid diagnosis was used to confirm whether those lesions were pathologically negative or not. The extent of the disease was finally confirmed by postoperative histologic findings. The ossicular chain was reconstructed with auricular cartilage, which was then set on top of the head of the stapes (type III tympanoplasty). The temporalis fascia was used to graft a new tympanic membrane. The anterior portion of the graft was sandwiched between the glenoid fossa and the temporomandibular joint capsule, and the rest was then placed over the columella and facial recess. This enabled the new eardrum to be stabilized

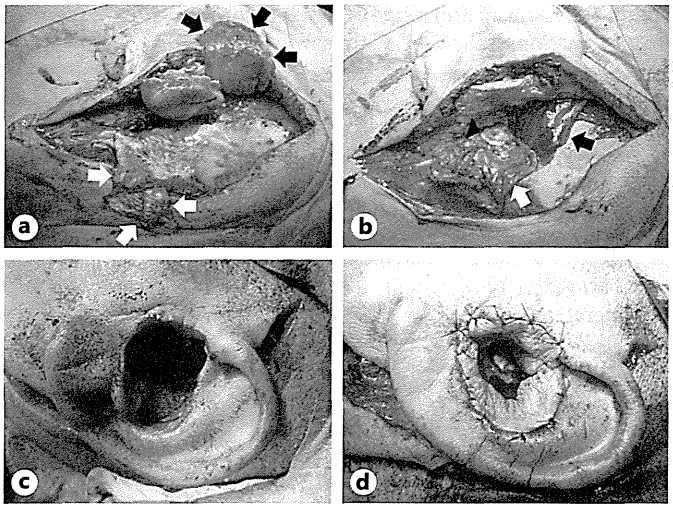

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Fig. 1. The anteriorly based temporalis muscle-pedicled flap (black arrow) and the inferiorly based periosteal-pedicled flap (white arrow) were prepared (**a**). The temporalis fascia was used to graft a new tympanic membrane (black arrowhead) and the new ear canal was reconstructed as the exposed bone was covered with these local-pedicled flaps in the reconstruction of the EAC without STSGs (**b**, **c**). STSGs were placed circumferentially to constitute the new ear canal, and the periosteal and muscle flaps were laid over these as a graft bed (**d**).

and the creation of a gap of several millimeters between the graft and the promontory, resulting in an air-containing middle ear space. Preservation of the temporomandibular joint capsule played an important role in preventing fat tissue around the joint from herniating into the middle ear and ear canal. Other temporalis fascia was placed over the posterior wall of the intact capsule for reinforcement. The new ear canal was then reconstructed, with the exposed bone covered with the inferiorly based periosteal-pedicled flap and the anteriorly based temporalis muscle-pedicled flap (fig. 1b, c). These local-pedicled flaps and the graft were fixed with fibrin glue. Chitin wound-protective materials were applied to these flaps in the new EAC and were expected to promote wound healing and epithelialization (w/o STSG group).

In cases in which consent was obtained, an STSG (0.18 mm thick, 6 × 4 cm) was obtained from the upper thigh using a dermatome. The STSG was placed circumferentially to constitute the new ear canal, and was laid over the periosteal and muscle flaps as a graft bed. The medial edge of the STSG slightly overlapped the temporalis fascia, and the lateral edge was sutured (fig. 1d). Gel foam was used to hold the fascia and the STSG of the new eardrum in place so as to reproduce the anterior tympanomeatal angle. Gauze was then placed into the new EAC to hold the STSG (STSG group).

Follow-Up

The gauze packing was removed 1 week after surgery. Dry ear precautions were enforced until the canal was fully epithelialized. Subsequent clinical visits were scheduled every 1–3 months for the first year, every 3–6 months for the second year, and every 6 months thereafter. CT, MRI, and/or ^{18}FDG-PET/CT were carried out every 6–12 months for up to 5 years after treatment. Because scar tissue after surgery was often hard to distinguish from recurrent carcinoma, we used enlargement of space-occupying lesions as a means of differentiation.

Audiometric Data

Audiometry was performed by experienced audiologists using a pure-tone audiometer (AA-76; RION Co., Japan) in a soundproof booth. The pure-tone thresholds for each ear were determined at frequencies of 125, 250, 500, 1,000, 2,000, 3,000, 4,000, 6,000 and 8,000 Hz for air conduction, and at 250, 500, 1,000, 2,000, 3,000, 4,000 and 6,000 Hz for bone conduction with masking as appropriate. Hearing tests were performed multiple times at clinical examinations before and after surgery, most commonly after 1 month, 3, 6 and 12 months. The audiological data used for our calculations in this article were the preoperative hearing thresholds and the most recent postoperative hearing thresholds obtained at least 12 months after surgery. The hearing outcome was evaluated based on pure-tone audiograms using the Committee on Hearing and Equilibrium guidelines of the American Academy of Otolaryngology-Head and Neck Surgery for the evaluation of the results of treatment of conductive hearing loss [American Academy of Otolaryngology-Head and Neck Surgery Foundation, 1995]. Pure-tone air and bone conduction thresholds were obtained, with thresholds at 500, 1,000, 2,000 and 3,000 Hz used to calculate the pure-tone averages. If 3,000 Hz was not tested, 4,000 Hz was substituted for the calculation of the pure-tone averages. Air and bone conduction averages from the same test were used to calculate the air-bone gaps (ABGs). A successful hearing result was defined as a postoperative ABG of 30 dB or less. Sensorineural hearing loss was defined as a high-frequency pure-tone bone conduction average (measured at 1,000, 2,000, and 4,000 Hz) that was more than 10 dB worse than the preoperative value.

Questionnaires

In this study, the postoperative QOL of patients was evaluated using the Glasgow Benefit Inventory (GBI). The GBI is a patient-oriented outcome instrument that has been demonstrated to be sensitive to changes in health status after otorhinolaryngological interventions [Robinson et al., 1996]. The GBI questions contain 18 items and the response to each question is based on a five-point Likert scale ranging from a large deterioration in health status through to a large improvement in health status. The total score for each respondent is between 18 and 90. These scores are then transposed into a benefit scale ranging from −100 to +100 following a simple mathematical formula (the raw score is divided by 18, 3 is subtracted and the result is multiplied by 50). A positive score indicates an improvement in QOL, a negative score indicates deterioration in QOL, and a score of zero indicates no change. The greater the positive or negative score, the larger the change in QOL. Three subscale scores for general health (12 questions), social support (3 questions) and physical health (3 questions), as well as an overall GBI score were calculated.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 12.0; SPSS Inc., Chicago, Ill., USA). Statistical differences were analyzed using the Mann-Whitney U test, with a p value of less than 0.05 considered statistically significant.

Results

Subject Profiles

Eighteen patients with early-stage EAC carcinoma were initially treated with LTBR at our institution between January 2006 and December 2012. Of these, 3 patients were excluded because they received postoperative adjuvant radiotherapy with or without chemotherapy. Thus, a total of 15 patients met the inclusion criteria for this analysis.

The study population consisted of 6 males and 9 females, ranging in age from 29 to 86, with a median age of 64 years. Twelve patients were categorized as stage I (T1N0) and 3 patients were stage II (T2N0). The histopathologic diagnosis was squamous cell carcinoma in all patients. The follow-up period ranged from 12 to 96 months, with a median of 32 months. No patients were lost during follow-up. The STSG group comprised 8 patients and the w/o STSG group 7 patients. There were no differences in age, gender distribution, stage or follow-up period between the two groups.

Survival Outcome

All patients in both groups have survived without locoregional or local recurrence. No distant metastasis has been observed, and there has been no significant morbidity or mortality.

Hearing Outcome

Table 1 shows the mean and range of ABGs in the STSG and w/o STSG groups. There were no significant differences in the mean ABG before surgery between the two groups of patients. In the STSG group, the mean ABG improved from 30.8 dB preoperatively to 19.8 dB at the most recent postoperative audiogram. Meanwhile, in the w/o STSG group, the mean ABG worsened from 35.0 to 45.7 dB. A comparison of the mean ABGs after surgery showed that in the STSG group was significantly lower than that in the w/o STSG group ($p < 0.001$).

The success rate for postoperative hearing was 75.0% in the STSG group, which was significantly higher than that in the w/o STSG group ($p = 0.014$). Unfortunately, no patients in the w/o STSG group showed improved hearing after surgery.

Complications

Table 2 summarizes complications observed in the STSG and w/o STSG groups. All patients in the w/o STSG group suffered stenosis. Ultimately, this resulted in closure of the EAC within fewer than 10 months after surgery (fig. 2a). In contrast, all patients in the STSG group showed preservation of the new EAC for more than 12 months after surgery (fig. 2b). There were significant differences in the incidence rate of stenosis and closure of the EAC between the two groups of patients

Table 1. The mean and range of ABGs before and after surgery for reconstruction of the EAC with or without STSGs

	STSG group	w/o STSG group	p value
ABG (mean ± SD), dB			
Preoperative	30.8±9.3	35.0±11.9	0.694
Postoperative	19.8±13.1	45.7±4.7	<0.001
ABG range, n (%)			
Preoperative			
0–10 dB	1 (12.5)	0 (0)	
11–20 dB	0 (0)	1 (14.3)	
21–30 dB	3 (37.5)	2 (28.6)	
31≤ dB	4 (50.0)	4 (57.1)	
Postoperative			
0–10 dB	3 (37.5)	0 (0)	
11–20 dB	2 (25.0)	0 (0)	
21–30 dB	1 (12.5)	0 (0)	
31≤ dB	2 (25.0)	7 (100)	

SD = Standard deviation.

Statistical differences were analyzed using the Mann-Whitney U test.

Table 2. Postoperative complications in the reconstruction of the EAC with or without STSGs

Complications	STSG group	w/o STSG group	p value
Stenosis of the EAC	0 (0)	7 (100)	<0.001
Closure of the EAC	0 (0)	7 (100)	<0.001
Granulation tissue	1 (12.5)	0 (0)	0.694
Lateralization of the TM	1 (12.5)	0 (0)	0.694
TM perforation	0 (0)	0 (0)	–
Infection	0 (0)	0 (0)	–
Necrosis	0 (0)	0 (0)	–
SNHL	0 (0)	0 (0)	–
Facial palsies	0 (0)	0 (0)	–

Number and percent (in parentheses) of patients with complications. TM = Tympanic membrane; SNHL = sensorineural hearing loss.

Statistical differences were analyzed using the Mann-Whitney U test.

($p < 0.001$). Although no patients in the STSG group showed tympanic membrane perforation, 1 patient revealed granulation tissue on the new tympanic membrane and 1 showed lateralization of the tympanic membrane. No patient in either group experienced infection, necrosis, sensorineural hearing loss or facial palsies.

Quality of Life

Figure 3 shows the mean overall GBI score as well as the three subscale scores for the STSG and w/o STSG groups. Those for the STSG group were found to be +37.9 (95% confidence interval, CI, +30.1 to +45.7), +36.0 (95% CI, +28.9 to +43.1), +56.3 (95% CI, +36.3 to +76.3) and +39.6 (95% CI, +13.2 to +66.0), respectively. Meanwhile, those for the w/o STSG group were found to be +9.1 (95% CI, −4.9 to +23.1), +0.6 (95% CI, −8.5 to +9.7), +23.8 (95% CI, −1.6 to +49.2) and +16.7 (95% CI, +5.3 to +28.1), respectively. A comparison of the mean GBI scores between the two groups of patients revealed that the overall and general health scores in the STSG group were significantly higher than those in the w/o STSG group ($p = 0.021$, $p = 0.001$).

Outcomes of Excluded Patients

The 3 patients who were excluded from this analysis were evaluated as stage II (T2N0). They received postoperative adjuvant radiotherapy at a total dose of 60 Gy with or without chemotherapy based on the presence of postoperative histologically positive margins. Of these, 2 patients were treated by the surgical reconstruction of the EAC w/o STSGs, and 1 patient underwent surgical reconstruction with STSG. The follow-up period ranged from 24 to 34 months. All 3 patients have survived without recurrence to date. After postoperative radiotherapy, delayed wound healing and granulation tissue appeared in the new EAC and ear-draining was maintained for several months. None experienced severe side effects, such as bone exposure, bone necrosis, brain stem damage, brain abscess or facial palsy. Ultimately, they all suffered closure of the EAC within fewer than 6 months after postoperative radiotherapy and their postoperative ABGs worsened in comparison to the preoperative values.

Discussion

Surgery with or without radiotherapy is widely accepted as the standard treatment for stage I and II EAC carcinoma, and previous reports have shown a depressingly poor prognosis for patients treated with radiother-

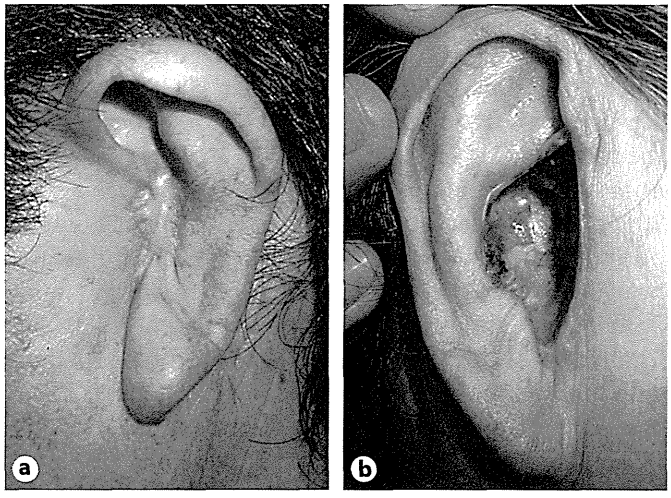

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Fig. 2. All patients in the reconstruction of the EAC w/o STSG group showed closure of the EAC within fewer than 10 months after surgery (**a**). All patients in the reconstruction of the EAC with STSG group showed preserved conformation of the new EAC for more than 12 months after surgery (**b**).

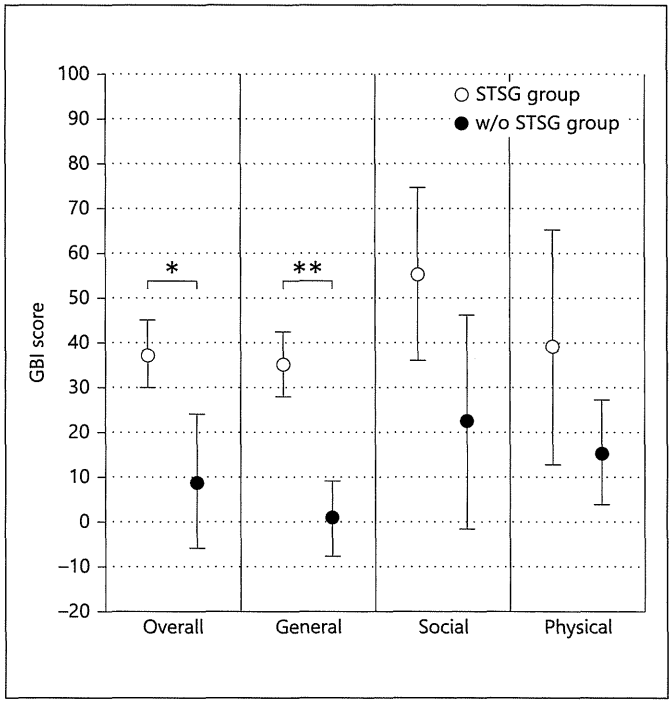

Fig. 3. The mean overall GBI score as well as the three subscale scores for the STSG and w/o STSG groups. The error bars indicate 95% CI for each graph. Statistical differences were analyzed using the Mann-Whitney U test. * $p = 0.021$, ** $p = 0.001$.

apy alone or salvage surgery after radiotherapy [Kunst et al., 2008; Moody et al., 2000; Nyrop and Grøntved, 2002]. Sleeve resection, local canal resection (LCR) and LTBR are the most frequently applied surgical procedures in the management of patients with early-stage EAC carcinoma [Kunst et al., 2008; Yin et al., 2006; Zhang et al., 2013]. Sleeve resection and LCR have no associated risk of affecting the adjacent neurovascular structures, and hearing is preserved postoperatively. However, it has been reported that patients who underwent LTBR had lower risks of positive margins and recurrence than did patients who underwent LCR [Kunst et al., 2008; Zhang et al., 2013]. Thus, the indication for sleeve resection and LCR is limited to lesions confined to the cartilaginous EAC. In the current study, all T1 lesions in the 12 patients involved the bony EAC; therefore, LTBR was selected in each case.

As early-stage carcinoma of the EAC can be generally cured by LTBR without postoperative radiotherapy, preservation of hearing ability and improvement in the QOL should be considered in selecting the treatment process [Hoshikawa et al., 2012; Iida et al., 2013; Koshima et al., 2004; Zhang et al., 2013]. In the absence of tumor invasion of the middle ear, it is possible to carefully separate the incus from the incudostapedial joint and preserve the stapes. Tympanoplasty to reconstruct the ossicular chain can be performed using a standard approach. However, since LTBR removes the entire EAC and tympanic annulus, care must be exercised to stabilize the anterior tympanic membrane by sandwiching the graft between the glenoid fossa and the temporomandibular joint capsule. In the current study, the postoperative mean ABG in the STSG group was found to be significantly lower than that in the w/o STSG group ($p < 0.001$). Moreover, the success rate for hearing in the STSG group was significantly higher than that in the w/o STSG group ($p = 0.014$). These results suggest that an adequate technique for reconstruction of the EAC, in addition to tympanoplasty, is essential to a successful hearing outcome.

Reconstruction of the EAC involves various techniques such as the creation of local-pedicled flaps, free flaps and skin grafts [Bell, 1988; Hoshikawa et al., 2012; Iida et al., 2013; Koshima et al., 2004]. As local flaps are limited in terms of size and mobility, it is difficult to reconstruct the entire EAC and cover a circumferential defect with a single local flap, necessitating dual local flaps or the concomitant use of skin grafting [Bell, 1988]. Moreover, reconstruction with local flaps alone has many shortcomings, such as contracture, stenosis, delayed wound healing, chronic infection, and bone exposure [Gal et al., 1998], resulting in conductive hearing loss and otorrhea. Meanwhile, the advantages of the free-flap methods lie in the prevention of these complications. Free flaps offer a durable lining with fewer limitations in terms of size and mobility [Iida et al., 2013]. However, conventional free flaps, including radical forearm flaps, are too thick for lining the defect [Iida et al., 2013]. STSG has the advantages of technical simplicity and shorter operation time [Hoshikawa et al., 2012; Iida et al., 2013; Koshima et al., 2004]. Although stenosis and closure of the EAC occurred in all patients in the w/o STSG group, all patients in the STSG group showed preserved conformation of the new EAC. Faster epithelialization and engraftment were observed in comparison with local flap use alone, leading to less stenosis and contracture of the reconstructed EAC. These local-pedicled flaps fulfilled a role as a graft bed, and blood supply from the graft bed to the free skin graft may be important for successful graft survival.

Enlargement of the EAC may lead to cosmetic problems. However, the mean overall and general health GBI scores in STSG group were significantly higher than those in the w/o STSG group ($p = 0.021$, $p = 0.001$). Additionally, all patients in the STSG group have accepted their new EAC. Some patients in the w/o STSG group were offered the use of bone-anchored hearing aids and other vibratory aids to overcome conductive hearing loss and improve directional hearing. However, they were less inclined to accept these devices due to financial problems and the overall aesthetics, such as the need for an external screw behind the auricle and the bulky design of the external sound processor. Thus, maintaining the conformation of the new EAC and preservation of hearing ability have significant advantages in terms of patient QOL.

Another advantage in keeping the conformation of the new EAC is the ease of postoperative access to and observation of lesions during the follow-up period. Closure of the EAC provides an oncological disadvantage in that the surgical scarring was often indistinguishable from residual or recurrent disease based on imaging techniques such as CT and MRI.

In conclusion, early-stage EAC carcinoma can be generally cured by complete surgical resection without postoperative radiotherapy, and higher 5-year survival rates are expected. Thus, the goal of treatment should not only be to accomplish tumor resection from an oncological standpoint but also to preserve hearing ability to improve the QOL for patients. Adequate methods for reconstruction of the EAC in addition to tympanoplasty are neces-

sary, as an STSG rolled up onto a local-pedicled flap provides an opportunity for promoting epithelialization and engraftment, while maintaining conformation of the new EAC. This technique is useful both in terms of hearing preservation and observation of locoregional lesions after surgery. Because of the rarity of EAC carcinoma, it has been difficult to perform large prospective series or multi-institutional studies. Thus, there are some limitations of the current study, such as small sample size and retrospective design. However, the clinically beneficial trend in hearing preservation after LTBR is evident and should be confirmed in future trials.

Disclosure Statement

We have no financial conflicts of interest and no financial support to declare. No conflicts of interest exist for any author.

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Effect of local extension sites on survival in locally advanced maxillary sinus cancer

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ABSTRACT: *Background.* We analyzed the effects of local extension sites on survival in patients with locally advanced maxillary sinus cancer.

Methods. The criteria for inclusion in this study were as follows: (1) previously untreated maxillary sinus cancer; (2) squamous cell carcinoma; (3) T4 disease; and (4) curative-intent treatment. The data for 118 patients were obtained from 28 institutions across Japan and analyzed for overall survival and local control rates by local extension site.

Results. Sites with a poor prognosis included the cribriform plate, dura, nasopharynx, middle cranial fossa, and cranial nerves other than V2. There was a significant correlation among these sites, except for the cranial nerves. Additionally, the hard palate was the only site that correlated with nodal involvement and showed a poor treatment outcome.

Conclusion. Even in cases presenting with similar T4 maxillary sinus cancer, treatment should be performed in consideration of the local extension site. © 2013 Wiley Periodicals, Inc. *Head Neck* **36:** 1567–1572, 2014

KEY WORDS: maxillary sinus cancer, total maxillectomy, radiation and intra-arterial cisplatin (RADPLAT), local extension site, hard palate

INTRODUCTION

Maxillary sinus cancer accounts for 3.6% of all head and neck cancers in Japan.[1] Because of the anatomic limitations in making an early diagnosis and the absence of symptoms in early-stage disease, a large number of maxillary sinus cancers are already at an advanced stage at the time of initial presentation. Most advanced cases require radical surgery with or without a complete resection of the contents of the orbit; however, this results in significant disfigurement and impairment of function. In order to reduce the complications associated with radical resection, trimodality therapy, consisting of partial maxillectomy, intra-arterial chemotherapy, and radiotherapy, has also been used for the treatment of maxillary sinus cancer in many institutions in Japan.[2,3]

Among nonsurgical treatments, chemoradiotherapy (CRT) has been reported to improve the survival rate compared to radiotherapy alone for unresectable squamous cell carcinomas (SCCs) of the head and neck.[4–6] However, CRT does not necessarily lead to satisfactory treatment outcome in cases of maxillary sinus cancer. Recently, superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy has been performed for the patients with locally advanced maxillary sinus cancer in several institutions and favorable results, in terms of survival, have been reported.[7–9]

As for the factors affecting prognosis in patients with maxillary sinus cancer, Bhattacharyya[10] reported that age, T classification, N classification, tumor grade, histopathology, and radiation therapy were all independent poor prognostic factors. Airoldi et al[11] also reported that T classification and histology have a clear impact on survival in sinonasal cancer. T classification and histological type are the most important factors in local control; however, most maxillary sinus cancers present as T4 classification SCCs.[10,11] Therefore, the eligibility criteria in this study were limited to T4 disease and SCC. Furthermore, the difficulties associated with the treatment of locally advanced tumors are expected to differ according to tumor progression site, even in cases with the same T classification. In this study, we focused on the sites into which the primary tumor had invaded and analyzed local

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TABLE 1. T and N classifications ($n = 118$).

T classification	No. of patients by N classification						Total
	0	1	2a	2b	2c	3	
T4a	60	2	0	9	2	0	73
T4b	35	4	0	3	3	0	45
Total	95	6	0	12	5	0	118

extension factors affecting survival and local control for patients with locally advanced maxillary sinus cancer.

MATERIALS AND METHODS

Patients

The inclusion criteria for this study were as follows: (1) previously untreated maxillary sinus cancer; (2) histological proof of SCC; (3) T4a or T4b disease; and (4) curative-intent treatment. The data for 118 patients were obtained from 28 institutions belonging to the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group between January 2006 and December 2007. Of the 118 patients, 87 were men and 31 were women. The median patient age was 64 years (range, 30–84 years). The T and N classifications of these patients are shown in Table 1. The median follow-up period for the survivors was 4.3 years (range, 0.2–5.9 years).

Initial treatment for the primary tumor

The initial therapeutic strategy was classified according to the treatment for the primary tumor (Table 2). Surgical treatment was categorized into total maxillectomy and partial maxillectomy, with total maxillectomy including extended total maxillectomy with simultaneous excision of an eyeball and skull base surgery. "Trimodality therapy," consisting of partial maxillectomy, intra-arterial chemotherapy, and radiotherapy, was categorized as partial maxillectomy. Surgery in which the anterior wall of the maxillary sinus was opened and necrotic tumor tissue in the maxillary sinus was curetted was also categorized as partial maxillectomy. The superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy was defined as radiation and intra-arterial cisplatin (RADPLAT), whereas intravenous chemotherapy with concomitant radiotherapy was defined as intravenous chemotherapy with concomitant radiotherapy (IV-CRT). Patients undergoing any form of surgery as the initial treatment were categorized as either total or partial maxillectomy even if RADPLAT or IV-CRT was performed as part of the preoperative or postoperative therapy.

TABLE 2. Initial therapeutic strategy.

	No. of patients (%)
Total maxillectomy	39 (33)
Partial maxillectomy	25 (21)
RADPLAT	22 (19)
IV-CRT	19 (16)
Others	13 (11)

Abbreviations: RADPLAT, radiation and intra-arterial cisplatin; IV-CRT, intravenous chemotherapy with concomitant radiotherapy.

Local extension sites

In this study, the detailed anatomic sites into which the primary tumor had extended were retrospectively evaluated by CT and MRI. The local extension sites were classified according to the 7th edition of the Union for International Cancer Control staging system (Table 3). As only 2 cases had invasion into the brain and no case showed any involvement of the clivus, the brain and clivus were excluded from this analysis. The patients with brain invasion were categorized together with those showing dural extension.

Statistical analysis

Overall survival and local control rates were calculated using the Kaplan–Meier method and were analyzed using the log-rank test. In this study, sites meeting the following criteria were defined as poor prognostic sites: (1) a statistically significant difference in overall survival rate and (2) the overall survival rate in the site with tumor extension was <30%. Correlations between the sites of tumor progression were tested using the chi-square test, and the degree of correlation was examined using the φ correlation coefficient. A 2-tailed p value $< .05$ was considered statistically significant. Statistical analyses were performed using XLSTAT 2011 (Addinsoft, New York, NY).

RESULTS

Overall survival rate for all patients

The 5-year overall survival rate was 49.8% for all patients included in this study (Figure 1). The 5-year overall survival rate was 29.6% for patients with neck lymph node metastasis at the initial presentation and

TABLE 3. Local extension factors.

	T2	T3	T4a	T4b
Superomedial	Middle nasal meatus	Ethmoid sinuses	Cribriform plate Frontal sinus	Dura
Superior			Anterior orbital contents	Orbital apex
Posterior		Posterior wall Pterygoid fossa	Pterygoid plates Sphenoid sinus	Nasopharynx Middle cranial fossa
Lateral			Infratemporal fossa	
Inferior	Hard palate			
Anterior		Subcutaneous tissue	Skin of cheek	
Cranial nerve				Other than V2

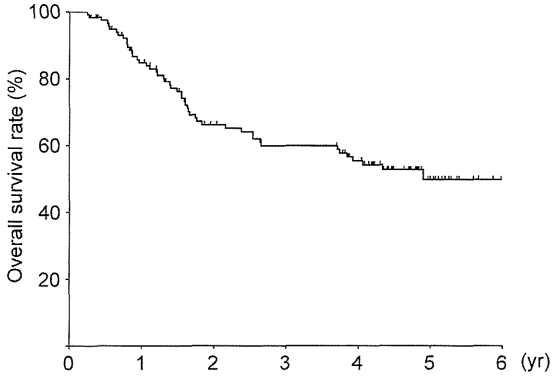

FIGURE 1. Overall survival rate for all patients.

53.5% for those without nodal involvement (p = .113; Figure 2).

Overall survival and local control rates by local extension site

Table 4 shows the 5-year overall survival and local control rates by local extension site. The local extension sites found to have a statistically significant difference from the overall survival rate were the ethmoid sinuses, cribriform plate, dura, sphenoid sinus, nasopharynx, middle cranial fossa, and cranial nerves other than V2. In terms of local control rate, sites consisted of the middle nasal meatus, dura, and hard palate. Of those sites with tumor invasion, the cribriform plate, dura, nasopharynx, middle cranial fossa, and cranial nerves other than V2 were considered to be poor prognostic sites.

Correlations among local extension and poor prognostic sites or neck lymph node metastasis

As the local extension sites examined in this study are anatomically close to each other, locally advanced tumors can easily extend into several adjacent sites around the maxillary sinus. Therefore, the correlations among local extension and poor prognostic sites or neck lymph node metastasis were examined using the chi-square test. The results showed that there were significant correlations among the cribriform plate, dura, nasopharynx, and middle cranial fossa (Table 5). Among those sites, the φ correlation coefficient, which shows the degree of correlation, was over 0.4 between the middle cranial fossa and dura, and between the middle cranial fossa and nasopharynx. Similarly, there were strong correlations between the cribriform plate and frontal sinus, and between the cribriform plate and sphenoid sinus. In contrast, cranial nerves other than V2 showed no correlation with the other poor prognostic sites, but showed significant correlations with the orbital apex, pterygoid fossa, and pterygoid plates. The hard palate, which showed a statistically significant difference in terms of local control rate, was correlated to the middle cranial fossa and neck lymph node metastasis.

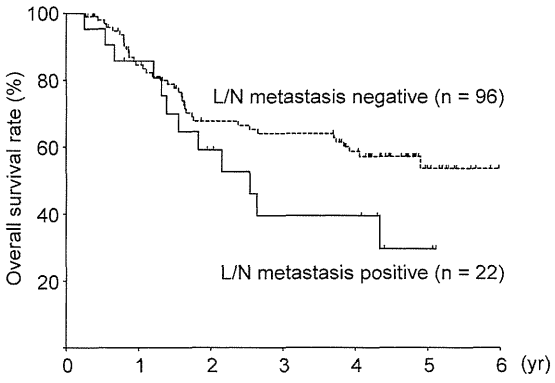

FIGURE 2. Overall survival rate for patients with or without lymph node metastasis.

Overall survival rate by initial treatment for patients with tumor extension into poor prognostic sites

Forty-eight of the total 118 patients had tumors developing into at least one of the 5 poor prognostic sites. Nine of these patients underwent total maxillectomy and 11 underwent partial maxillectomy. RADPLAT was performed for 10 patients and IV-CRT was performed for 11 patients. Table 6 shows the patients' initial treatment by local extension site. Although patients with invasion into the dura received nonsurgical treatment more frequently than surgical treatment, there was no significant bias overall. The 5-year overall survival rate for patients treated with total maxillectomy, partial maxillectomy, RAPLAT, and IV-CRT were 75.0, 22.7, 31.7, and 20.0%, respectively (Figure 3).

DISCUSSION

Our results showed that all poor prognostic sites, except for the cribriform plate, were factors defined as T4b. Although there was no significant difference in survival rate associated with orbital apex invasion, which is also a factor defined as T4b, the 5-year overall survival rate was as low as 30.4% (p = .087). T4b disease generally indicates an unresectable tumor in head and neck cancer, whereas some of them can be resected with curative intent in maxillary sinus cancer. However, our results showed that patients with maxillary sinus cancer with T4b disease had a poor prognosis similar to those with other head and neck cancers. All poor prognostic sites, except for the cranial nerves other than V2, were correlated with each other, as the sites were generally adjacent to each other within a limited anatomic region. Therefore, it was impossible to identify independent factors for poor prognostic sites. On the other hand, among the sites defined as T4a, 5-year overall survival rates for tumor extension into the frontal sinus, anterior orbital contents, and infratemporal fossa were relatively favorable (58.3%, 47.8%, and 49.4%, respectively). Apart from a correlation between the frontal sinus and cribriform plate, those sites had no correlations with the poor prognostic sites. If a tumor is limited to the frontal sinus, anterior orbital contents, or infratemporal fossa, a relatively good prognosis can be expected, even in cases with T4a disease. Dulguerov et al[12] reviewed 220 patients with nasal and paranasal sinus cancer treated between 1975 and 1994 and reported that patients with an extension into the