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Equivalence Randomized Trial to Compare Treatment on the Basis of Sentinel Node Biopsy Versus Neck Node Dissection in Operable T1-T2N0 Oral and Oropharyngeal Cancer

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abstract

PURPOSE Sentinel node (SN) biopsy is accurate in operable oral and oropharyngeal cT1-T2N0 cancer (OC), but, to our knowledge, the oncologic equivalence of SN biopsy and neck lymph node dissection (ND; standard treatment) has never been evaluated.

METHODS In this phase III multicenter trial, 307 patients with OC were randomly assigned to (1) the ND arm or (2) the SN arm (experimental arm: biopsy alone if negative, or followed by ND if positive, during primary tumor surgery). The primary outcome was neck node recurrence-free survival (RFS) at 2 years. Secondary outcomes were 5-year neck node RFS, 2- and 5-year disease-specific survival (DSS), and overall survival (OS). Other outcomes were hospital stay length, neck and shoulder morbidity, and number of physiotherapy prescriptions during the 2 years after surgery.

RESULTS Data on 279 patients (139 ND and 140 SN) could be analyzed. Neck node RFS was 89.6% (95% CI, 0.83% to 0.94%) at 2 years in the ND arm and 90.7% (95% CI, 0.84% to 0.95%) in the SN arm, confirming the equivalence with $P < .01$. The 5-year RFS and the 2- and 5-year DSS and OS were not significantly different between arms. The median hospital stay length was 8 days in the ND arm and 7 days in the SN arm ($P < .01$). The functional outcomes were significantly worse in the ND arm until 6 months after surgery.

CONCLUSION This study demonstrated the oncologic equivalence of the SN and ND approaches, with lower morbidity in the SN arm during the first 6 months after surgery, thus establishing SN as the standard of care in OC.

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INTRODUCTION

T1-T2N0 squamous cell carcinoma of the oral cavity and oropharynx (OC) is treated by tumor surgery and elective neck lymph node dissection (ND) to detect and treat occult lymph node metastases.[1] Although ND is indispensable,[2] it has been associated with significant morbidity, which can be reduced by sentinel node (SN) biopsy.[3] This reliable diagnostic technique can be performed routinely[4,5] and has been proposed for this indication on the basis of the available evidence and expert consensus.[6] However, to our knowledge, there is no high-level evidence of the equivalence or noninferiority of SN biopsy in neck node management for this indication. The aim of the current trial was to assess the oncologic equivalence of SN biopsy and ND for OC by comparing the 2-year neck node recurrence-free survival (RFS) as primary outcome between patients who underwent SN biopsy (experimental arm) and those who underwent ND (standard arm). Secondary outcomes included 5-year neck node RFS, 2- and 5-year locoregional RFS, 2- and 5-year disease-specific survival (DSS), and 2- and 5-year overall survival (OS), as well as hospitalization length, shoulder and neck morbidity, and physiotherapy prescriptions during the post operative period.

METHODS

Trial Design and Oversight

The Senti-MERORL trial was a multicenter, randomized open-label prospective equivalence study.

Random Assignment

The two-arm random assignment was performed using small balanced blocks at each center, with a 1:1 ratio.

Patient Population

Eligible patients were adults with operable OC (cT1-T2N0 according to the 7th edition of the American

ASSOCIATED CONTENT

See accompanying editorial on page 3983

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Is the sentinel node (SN) biopsy technique effective and safe in patients with oral cavity and oropharynx T1-T2N0 cancer (OC)? Only a prospective equivalence randomized study can definitely answer this question by comparing neck dissection (the standard treatment) and SN biopsy.

Knowledge Generated

This study allowed us to strongly demonstrate the oncologic equivalence of these two strategies. Moreover, it showed that functional outcomes during the first year after surgery were better in the SN arm, suggesting a reduction in care consumption with the SN approach.

Relevance

The effective collaboration among nuclear medicine physicians, pathologists, and oncologic surgeons allows the proposal of SN biopsy as the standard of care for OC.

Joint Committee on Cancer/Union for International Cancer Control TNM classification,[7] which was used throughout the inclusion period), who were accessible to transoral radiotracer injection for lymphoscintigraphy and were without a history of head and neck (HN) cancer, neck surgery, or radiation therapy. All patients signed a written informed consent before enrollment. The inclusion criteria are listed in Appendix Table A1 (online only). N0 status was established by neck contrast-enhanced computed tomography (CT) or by neck magnetic resonance imaging (if contraindication for CT). Data were entered at each center using OpenClinica (Waltham, MA).

Trial Treatment

The standard arm ND included tumor surgery and homolateral elective ND (or bilateral if the tumor reached the median line; Protocol), followed by routine histopathologic lymph node analysis. The experimental arm included SN identification by radiotracer injection, followed by lymphoscintigraphy the day before or on the morning of the surgical intervention. During surgery, SNs were identified using an intraoperative portable gamma probe. Tumor invasion of SN (pSN+) was defined by the presence of at least one micrometastasis (MI; tumor tissue size between 200 μm and 2 mm) or one macrometastasis (MA; tumor tissue $>$ 2 mm).[8] Isolated tumor cells (ITC+, tumor tissue size $<$ 200 μm) on their own were not considered to be node invasion.[9,10] Intraoperative histopathologic analysis of SN was performed by imprint cytology or frozen section examination (left to the pathologist's choice). ND was advocated in the case of pSN+. If SN positivity was detected only after postsurgery step serial sectioning and immunohistochemistry analysis,[11] ND was performed during a second surgical procedure. Dissection was bilateral in the case of contralateral pSN+ or if bilateral drainage was observed by lymphoscintigraphy.[11] In both arms, adjuvant radiotherapy was planned if two or more lymph nodes (including the SN, if applicable) were pN+. Concomitant adjuvant chemoradiotherapy was proposed in the case of poor prognostic factors in the tumor, such as vascular or perineural invasion, or intrinsic tongue muscle invasion.

Outcomes

The primary outcome was the 2-year neck node RFS, determined by studying the isolated neck node recurrence rate. Primary tumor recurrence and the development of a second HN cancer were excluded from this criterion.

Secondary outcomes included (1) Locoregional RFS, determined by recording the number of isolated primary tumor recurrences, tumor and neck recurrences, and isolated neck recurrences; (2) DSS, determined by recording the number of deaths linked to primary cancer progression; (3) OS, determined by recording the number of deaths as a result of any cause; (4) hospitalization length of stay; (5) neck-shoulder functional morbidity, assessed using a self-report neck and shoulder impairment questionnaire and arm abduction test derived from those described in the literature[12]; and, (6) number of physiotherapy prescriptions.

Follow-Up Assessment

The oncologic follow-up was performed by the surgeon in charge of the patient every 2 months during the first year, every 4 months during the second year, and once per year during the next 3 years. This included a clinical examination at each visit and a neck-thorax CT scan at year 1 and year 2 after surgery. The functional follow-up was performed by the surgeon at months 2, 4, and 6 and at year 1 and year 2 after surgery.

Sample Size

The sample size was determined on the basis of the hypothesis of equivalence of the 2-year neck node recurrence

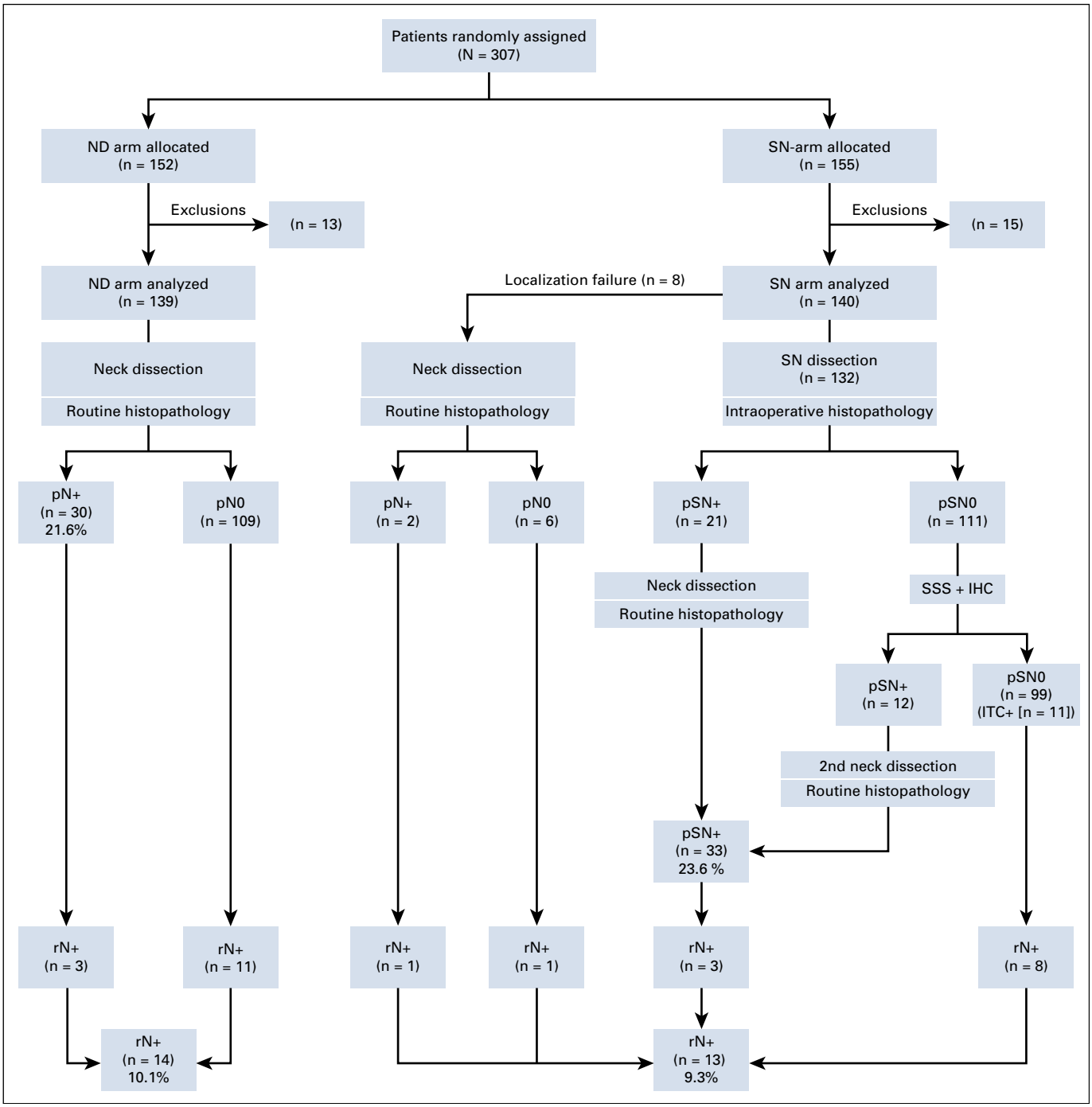

FIG 1. Patient inclusion in the neck dissection (ND) and sentinel node biopsy (SN) arms. Exclusion criteria were noninvasive tumor (diagnosis of severe dysplasia and in situ carcinoma without lamina propria invasion) or no respect/deviation from the protocol precluding the first outcome analysis (complete list in Table 1). Histopathologic status: pSN+, patient with at least one invaded SN; pSN0, patient without invaded SN; pN+, patient with invaded lymph node; pN0, patient with negative lymph node; rN+, patient with clinical neck relapse only (without primary tumor relapse or second primary tumor) and a mean follow-up of 4.9 ± 2.4 years; second neck dissection, patient in the SN arm with detection of SN invasion only during serial section staining and immunohistochemistry analysis and thus requiring a second surgery for ND (eg, false-negative results in the intraoperative histopathologic analysis); ITC+, patient in which SN had isolated tumor cells only, without micro- or macrometastasis in all analyzed lymph nodes. IHC, immunohistochemical analysis; SSS, step serial sectioning.

rate with an α risk of 5% (one-tailed test) and a power of 90%. According to data in the literature,[13] the neck recurrence at 2 years was 10% in patients undergoing ND. It was estimated that this rate should not exceed 20% (ie, $\delta = 10\%$) with the SN technique. Using a one-tailed test with these hypotheses, 310 patients in total were required. If data for 5% of patients were not exploitable, 328 patients needed to be included.

TABLE 1. Causes of Patients' Exclusion

Observation	Arm	Received Allocated Intervention	Cause of Exclusion
1	ND	Yes	High-grade dysplasia
2	ND	Yes	In situ carcinoma
3	ND	Yes	In situ carcinoma
4	ND	Yes	History of surgery for oral cavity cancer
5	ND	Yes	History of radiotherapy for oropharyngeal cancer
6	ND	Yes	R1 margins without tumor surgery completion
7	ND	Yes	In situ carcinoma
8	ND	Yes	In situ carcinoma
9	ND	No	Refusal of surgical treatment
10	ND	No	Radiotherapy decision by oncologist
11	ND	No	Refusal of random assignment (asked for SN)
12	ND	Yes	In situ carcinoma
13	ND	No	Withdrawal of patient consent
14	SN	Yes	Synchronous lung tumor
15	SN	Yes	High-grade dysplasia
16	SN	No	Urgent carotid surgery
17	SN	Yes	In situ carcinoma
18	SN	Yes	Erroneous inclusion: T4 tumor
19	SN	Yes	In situ carcinoma
20	SN	No	Refusal of random assignment (asked for ND)
21	SN	No	Refusal of random assignment (asked for ND)
22	SN	No	Investigator's decision without additional details
23	SN	Yes	In situ carcinoma
24	SN	Yes	In situ carcinoma
25	SN	No	ND despite ITC+ only
26	SN	No	Refusal of random assignment (asked for ND)
27	SN	Yes	In situ carcinoma
28	SN	Yes	Erroneous inclusion: T4 tumor

Abbreviations: ITC, isolated tumor cells; ND, neck dissection arm; SN, sentinel node biopsy arm.

Statistical Methods

The χ^2 test or Fisher's exact test was used to compare qualitative data, and the Wilcoxon rank-sum test was used for quantitative data. Means and standard deviations (SDs) were compared with the Student's *t* test. Patients with missing data (MD) were excluded from the analyses. Data were analyzed using an intention-to-treat analysis. The null hypothesis H_0: $(R_{SN} - R_{ND}) \geq 0.10$ was tested against the alternative hypothesis H_1: $(R_{SN} - R_{ND}) < 0.10$, where R_{SN} is the node recurrence rate in the SN arm and R_{ND} is the recurrence rate in the ND arm. The hypothesis H_0 represents the non-equivalence. The statistical analysis was performed using the classic methodology of equivalence trials.[14] Time origin was the time of first surgery. Data were censored at the date of last data collection in the case of no event occurrence. The survival curves were estimated in each arm using the Kaplan-Meier method and were compared with the log-rank test using SAS software version 9.4 (SAS Institute, Carey, NC).

RESULTS

Patients' Baseline Characteristics

The study included 307 patients who were enrolled at the 10 participant centers during 5 years, prolonging the inclusion period of 3 years and 3 months to approach the required number of patients (Fig 1). Twenty-eight patients were excluded, 13 in the ND arm and 15 in the SN arm (Table 1). The analysis therefore included 279 patients, 139 in the ND arm and 140 in the SN arm (ie, statistical power of 85.6%). The patients' clinical-pathologic features are listed in Table 2.

Procedural Characteristics

The mean number of dissected nodes per patient was 29.09 (SD, 14.99) in the ND arm (MD, 11) and 2.93 (SD, 1.42) in the SN arm (MD, 12). In the SN arm, 29 patients underwent neck node dissection during the primary tumor surgery because of SN biopsy technical failure (n = 8)

TABLE 2. Patients' Clinical-Pathologic Characteristics and Adjuvant Treatments

Characteristic	ND (n = 139)	SN (n = 140)	P
Age, years, mean ± SD	59.1 ± 10.9	60.8 ± 12.0	.20
Male sex	101 (72.7)	88 (62.8)	.08
Tumor location			
Oral cavity	119 (85.6)	124 (89.2)	.37
Oropharynx	20 (14.4)	15 (10.8)	
Missing data	0 (0.0)	1 (0.7)	
T stage			
cT1	91 (65.5)	88 (62.8)	.65
cT2	48 (34.5)	52 (37.1)	
N pathologic stage			
Not invaded	109 (79.0)	105 (75.0)	.73
Invaded without ENE	20 (14.5)	24 (17.1)	
Invaded with ENE	9 (6.5)	11 (7.9)	
Missing data	1 (0.7)	0 (0.0)	
Adjuvant treatment			
No adjuvant treatment	105 (75.5)	107 (76.4)	.46
Radiotherapy alone	24 (17.3)	17 (12.1)	
Chemoradiotherapy	6 (4.3)	10 (7.1)	
Brachytherapy	4 (2.9)	6 (4.3)	

NOTE. Data are presented as No. (%) unless indicated otherwise. The χ^2 test was used to compare qualitative data, and the Wilcoxon rank-sum test was used for quantitative data.

Abbreviations: ENE, extranodal extension; ND, neck dissection group; SN, sentinel node biopsy group.

precluding the node localization and surgical excision (failure rate, 5.7%) or because of detection of pSN+ by the intraoperative histopathologic analysis (n = 21 [15.9% of the 132 patients with successful SN biopsy]). ND was performed during a second surgical intervention in 12 patients in the SN arm in whom the intraoperative histologic analysis was negative. Level IIb dissection was performed in 26 of 33 pSN+ patients (79%). The sensitivity and negative predictive value of the intraoperative histologic analysis were 63.6% and 89.2%, respectively (Table 3). The first-line treatment was only surgery in 105 patients in the ND arm and 107 patients in the SN arm. Adjuvant treatments are listed in Table 2.

Outcomes

The mean follow-up was 4.95 ± 2.45 years (5.15 ± 2.33 years in the ND arm and 4.74 ± 2.55 years in the SN arm; $P = .15$, Wilcoxon rank-sum test). The pN stage of the dissected nodes, the pSN stage of the SNs, and the neck node recurrence stage (rN) rate are shown in Figure 1. During the follow-up, the presence of neck node recurrence (rN+) without relapse of the primary tumor or a second HN primary tumor was observed in 14 of 139 patients in the ND arm (10.1%) and in 13 of 140 patients in the SN arm (9.3%; $P = .82$; χ^2 test; Fig 1). The 2- and 5-year neck node RFS rates were 89.6% (95% CI, 0.83% to 0.94%) and 89.6% (95% CI, 0.83% to 0.94%) in the ND arm, and 90.7% (95% CI, 0.84% to 0.95%) and 89.4% (95% CI, 0.82% to 0.94%) in the SN arm (Fig 2A). The difference between arms in the 2-year neck node RFS was 1.1%, which was lower than the 10% hypothesis ($P < .01$), confirming the equivalence of the two strategies.

TABLE 3. Contingency Table for the Intraoperative SN Histopathologic Analysis and Definitive Histopathology Analysis

Histopathology	Definitive+	Definitive−	Total
Intraoperative+	21	0	21
Intraoperative−	12	99	111
Total	33	99	132

NOTE. Sensitivity = 63.6%, specificity = 100%, negative predictive value = 89.2%, and positive predictive value = 100%.

Abbreviation: SN, sentinel node biopsy.

Among the patients with rN+, 11 patients in the ND arm were classified initially as pN0 (10.1% of the 109 patients with pN0), and eight patients in the SN arm were pSN0 (8.1% of the 99 patients with pSN0; $P = .61$, χ^2 test; Fig 1). In the SN arm, the 11 patients with ITC+ did not show any neck node recurrence. One had a local tumor recurrence and another, a second HN primary tumor.

In the ND arm, 18 patients (12.95%) presented a second HN primary tumor, and 20 (14.39%) a local relapse (in one patient, the local tumor relapse was associated with node recurrence). Two patients progressed to metastatic disease, and four patients (2.88%) developed another cancer type.

In the SN arm, six patients (4.29%) developed another cancer type, 14 patients (10%) presented a second HN primary tumor, and 19 (13.57%) had a local tumor relapse (in three patients, this was associated with node recurrence). One patient progressed to metastatic cancer. The tumor relapse rate ($P = .84$) and relapse management ($P = .86$) were not significantly different between arms (data not shown).

Concerning the secondary end points, the 2- and 5-year locoregional RFS rates were 83.1% (95% CI, 0.75% to 0.89%) and 73.6% (95% CI, 0.64% to 0.81%) in the ND arm and 81.8% (95% CI, 0.74% to 0.87%) and 76.3% (95% CI, 0.67% to 0.83%) in the SN arm (Fig 2B). The 2- and 5-year DSS rates were 95.5% (95% CI, 0.90% to 0.98%) and 88.6% (95% CI, 0.82% to 0.93%) in the ND arm and 93.0% (95% CI, 0.87% to 0.96%) and 87.1% (95% CI, 0.79% to 0.92%) in the SN arm (Fig 2C). The 2- and 5-year OS rates were 92.6% (95% CI, 0.87% to 0.96%) and 81.8% (95% CI, 0.74% to 0.88%) in the ND arm and 88.7% (95% CI, 0.82% to 0.93%) and 82.2% (95% CI, 0.74% to 0.88%) in the SN arm (Fig 2D). No significant difference was observed between arms

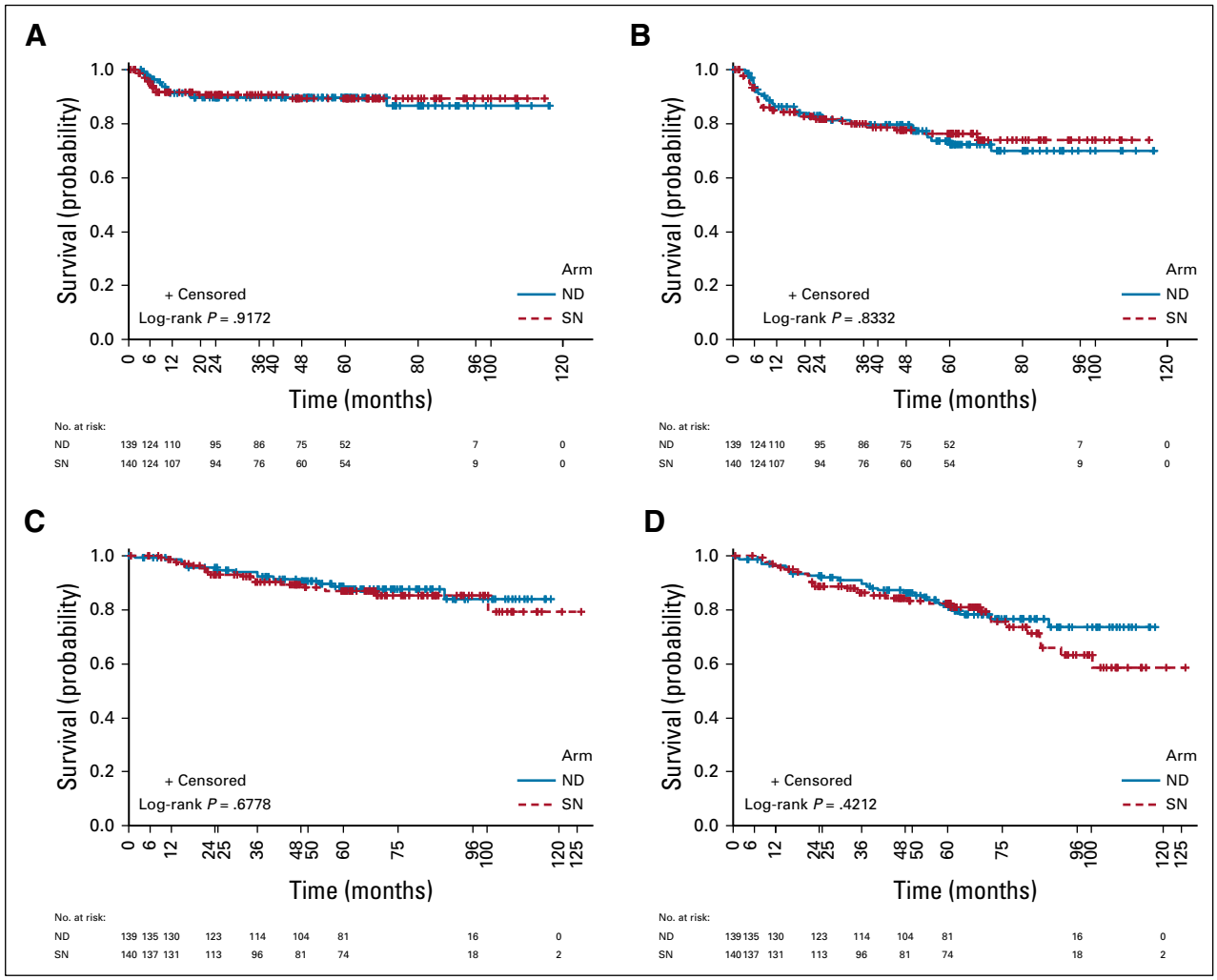

FIG 2. Comparison of the survival curves for the neck node dissection (ND) and sentinel node biopsy (SN) arms (log-rank test). (A) Neck node recurrence-free survival. (B) Locoregional recurrence-free survival. (C) Disease-specific survival (death related to the treated cancer). (D) Overall survival (regardless of the cause of death).

regarding neck node RFS ($P = .92$), locoregional RFS ($P = .83$), DSS ($P = .68$), or OS ($P = .42$).

The median (minimum-maximum) hospital stay length was 8 days (2-94 days) in the ND arm and 7 days (3-30 days) in the SN arm (Wilcoxon rank-sum test; $P < .01$). The mean stay was 10.4 days (SD, 9.13 days) in the ND arm and 8.09 days (SD, 4.52 days) in the SN arm (Student's t test; $P = .01$).

The results of the neck-shoulder impairment self-report questionnaire at months 2, 4, 6, and 12 after surgery are presented in Figure 3. Up to month 12, the scores of some items were significantly different between arms, but not at month 24 (data not shown).

The arm abduction test (at 180° without pain or effort) showed that this movement could be performed by 50.51% versus 71.03% of patients in the ND and the SN arm, respectively, at month 2 ($P < .01$; MD, 26%), 57.89% versus 74.29% at month 4 ($P = .01$; MD, 28%), 60.23% versus 76.29% at month 6 ($P = .02$; MD, 34%), 76.92% versus 84.95% at month 12 ($P = .18$; MD, 39%), and 78.38% versus 87.8% ($P = .11$; MD, 44%) at month 24.

The physiotherapy prescription rates were 33.33% versus 10.17% in the ND and SN arms, respectively, at month 2 ($P < .01$; MD, 18%), 37.74% versus 18.1% at month 4 ($P < .01$; MD, 20%), 31.96% versus 17.86% at month 6 ($P = .02$; MD, 25%), 20.65% versus 16.16% at month 12 ($P = .42$; MD, 32%), and 8.05% versus 9.3% at month 24 ($P = .77$; MD, 38%).

In the SN arm, the subgroup of 12 patients with node dissection during a second surgical intervention was compared with the subgroup of 21 patients with node dissection during the first surgery. No significant difference in any functional parameter was observed (data not shown).

DISCUSSION

The Senti-MERORL trial demonstrates the oncologic equivalence of SN for the treatment of OC relative to the

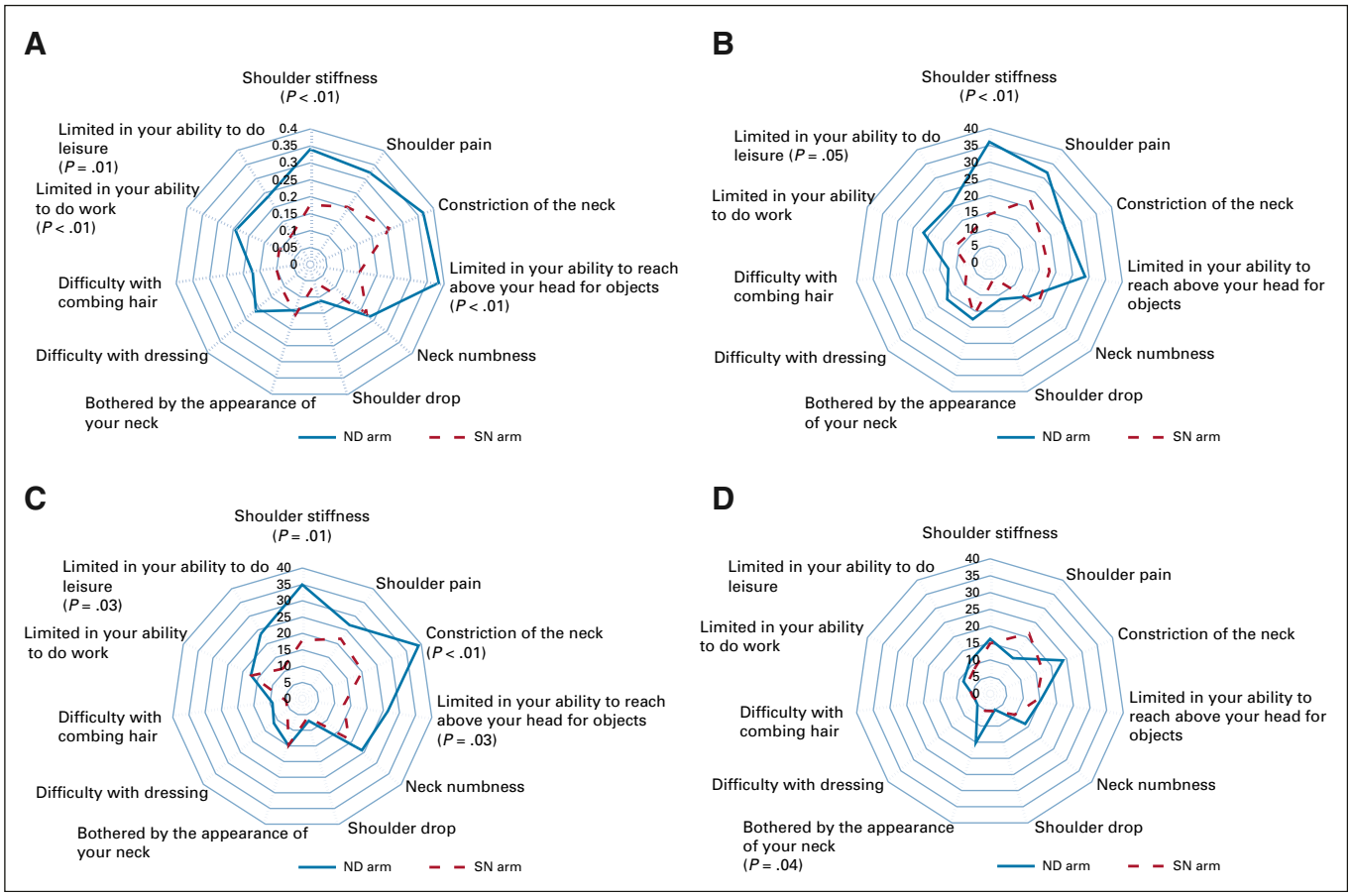

FIG 3. Radar plots showing the neck-shoulder impairment scale results (percentage of positive responses to the indicated questions) at (A) 2 months, (B) 4 months, (C) 6 months, and (D) 12 months after surgery. Data for the two arms were compared using the Fisher's exact test. ND, neck node dissection; SN, sentinel node biopsy.

reference strategy (ND). Patients showed the same rate of neck failure (approximately 10% in the two arms), consistent with previous data in the literature.[1,13] For equivalent neck RFS at 2 years ($P < .01$) and without any difference in locoregional disease control, DSS, and OS at 2 and 5 years, the functional results were superior and the median hospital length of stay was shorter in the SN arm. This establishes the SN strategy as the reference technique.

Despite a significant difference between arms, the median and mean hospital stay length were long in both arms.[15] This was mainly because of a health system policy that did not promote outpatient treatment and short hospitalization during the study period. Moreover, in some patients, hospitalization was long because of comorbidities and major complications.

The study strengths are its random assignment design, which allowed most of the selection biases to be overcome, and the mean follow-up period, which approached 5 years. The enrolled population was comparable to those usually described,[9] and both patients groups were fully comparable regarding all observed criteria. The mean number of lymph nodes analyzed in the two arms was in accordance with the usual recommendations,[1,6] as was the observed SN detection failure rate.[6] The number of patients who received adjuvant therapy was relatively high[15] but was balanced between arms; therefore, it should not influence the main results of the study. Moreover, the heterogeneity of participant centers (expert and nonexpert surgeons in SN biopsy) allowed the feasibility of the SN technique to be shown. Before study initiation, nonexpert surgeons underwent 1-day training and were asked to perform 10 completion neck dissection. However, the study was not designed to evaluate the proficiency in function of the surgeons. Civantos et al[16] reported negative predictive values of 100% and 95% for SN biopsy performed by trained surgeons and less experienced surgeons, respectively (Cohen's $\kappa = 0.90$), suggesting the feasibility of SN biopsy for low-risk OC.

Some limitations must be acknowledged. Although T1-T2N0 OC is common, the restrictive inclusion criteria hindered the enrollment of patients, and despite the extension of the inclusion period (5 years in total), inclusion was stopped at 307 patients instead of 328. Although the number of enrolled patients was slightly lower than the

required sample size, the statistical power for the primary end point was > 85%, which is considered adequate for equivalence testing.[14] The functional analysis was performed at close intervals during the first year after surgery. This allowed us to highlight a functional difference between arms that disappeared after the first 6 months for physiotherapy prescriptions and for the arm abduction test, and after 12 months for the item "bothered with the appearance of the neck" of the neck-shoulder impairment scale. This indicates that in the ND arm, neck-shoulder function morbidity is higher during the first year after surgery, but it is reversible in most cases. However, no functional evaluation was performed at baseline, precluding intragroup comparisons between baseline and the postsurgery assessments. Moreover, only selected items of the original neck and shoulder impairment scale were used. This precluded the calculation of a total score, as performed in the original publication,[12] and only the positive answer rates for each item were reported (Fig 3). Furthermore, the high percentage of MD concerning the postsurgery functional assessment (between 18% and 44%) reduced the statistical power of this analysis.

For the cost estimation, this study considered only the median and mean hospital stays, which were significantly shorter in the SN arm, and the postsurgery physiotherapy prescriptions. An ancillary medico-economic study on cost itemization and quality of life is currently under way.

Our study indicated that the main advantage of the SN technique is the reduction of neck surgery, with only 29.3% of patients in the SN arm undergoing neck dissection (41 of 140): 33 patients with pSN+ and eight patients with SN biopsy failure. neck dissection were able to be performed during the same surgical intervention in 29 of these patients (70.7%). Twelve false-negative results in the intraoperative histologic analysis led to a second intervention (8.6% of patients in SN arm). The low sensitivity of the intraoperative analysis for the diagnosis of occult metastasis reported here (63.6%) is in agreement with previous data in the literature.[17,18] Although frozen section analysis is generally used by histopathologists, imprint cytology also is accepted in the absence of clinical evidence and recent recommendations for a specific technique[6] Extensive, and thus more time-consuming, intraoperative SN analysis might enhance its sensitivity and decrease the number of patients who will undergo a second intervention. However, this would increase the duration and cost of the entire procedure. This point should be investigated in a medico-economic study. Moreover, molecular methods, which are more time and tissue consuming but also more sensitive, should be tested more widely in this setting.[19-21] The postsurgery functional results in the subgroup of patients who underwent a second surgery were not different from those of patients who had node dissection during the same intervention. This can be explained by the low number of patients who did not allow a robust analysis, or by the real absence of differences between these conditions.

Neck recurrence analysis showed that most events occurred during the first 24 months, thus validating the choice of 2-year RFS as the primary end point. However, the precise location of the neck recurrence (within or outside the surgery field) was not recorded in the case report form. Future studies should investigate the relapse mechanisms because they remain unclear in approximately 10% of patients, regardless of the pN status and risk factors.

Finally, ITC detection is controversial. In the Sentinel European Node Trial, the presence of ITC only, considered to be pathologic, led to ND. This group showed a better OS than did patients with MI+ and MA+ nodes[9]. In the current study, neck node recurrence and locoregional recurrence rates were not different in the 11 patients with ITC+ compared with the pSN0 group (data not shown). Therefore, the ITC+ status does not seem to require ND. In conclusion, this study establishes SN as the standard of care for the treatment of OC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Equivalence Randomized Trial to Compare Treatment on the Basis of Sentinel Node Biopsy Versus Neck Node Dissection in Operable T1-T2N0 Oral and Oropharyngeal Cancer

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

APPENDIX

TABLE A1. Inclusion and Exclusion Criteria

Inclusion criteria
> 18-year-old patient without upper age limit
Patient with health insurance
Signature of the informed consent form after information on the study
Patient not participating in another trial
Absence of any previous treatment of head and neck cancer
Primary squamous cell carcinoma of the oral cavity or oropharynx documented by biopsy with histopathologic analysis performed in the last month before inclusion
Operable tumor in function of the TNM stage (7th edition of the AJCC/UICC TNM classification[7]), tumor location, and patient's general health status
Stage T1 or T2
Stage N0 tumor that met the following criteria (21-day validity period): (1) absence of palpable lymphadenopathy at clinical examination by the investigator; (2) CT scan or MRI with injection of contrast product showing lack of suspicious adenomegaly, with node size < 1 cm and < 1.5 cm for level IIa, ovoid and homogeneous nodes, not enhanced by injection and showing no sign of perinodal invasion (fat, vessels, or muscles), absence of more than three grouped lymph nodes
Head and neck panendoscopy to exclude a second synchronous cancer and precisely establishing the T (21-day validity period)
Stage M0
Exclusion criteria
Not meeting one of the inclusion criteria
Treatment of other cancer
Noninvasive tumor: high-grade dysplasia, in situ carcinoma
Inadequate tumor excision: invaded margins without additional surgery to achieve R0 resection
Contraindication to sentinel node biopsy or lymph node dissection
Contraindication to radiotherapy
Contraindication to medical imaging
Known allergy or intolerance to the injected contrast product, particularly to Technetium-99
Pregnancy
Refusal to accept the full treatment, regardless of the random assignment arm
Follow-up not possible
Refusal to accept the follow-up and/or provide the necessary information for the study
Patient already treated for the tumor, with the exception of excision biopsy
Patient had chemotherapy or immunotherapy for another cancer within the last 6 months
Patient had a history of neck surgery and/or radiotherapy

Abbreviations: AJCC/UICC, American Joint Committee on Cancer/Union for International Cancer Control; CT, computed tomography; MRI, magnetic resonance imaging.