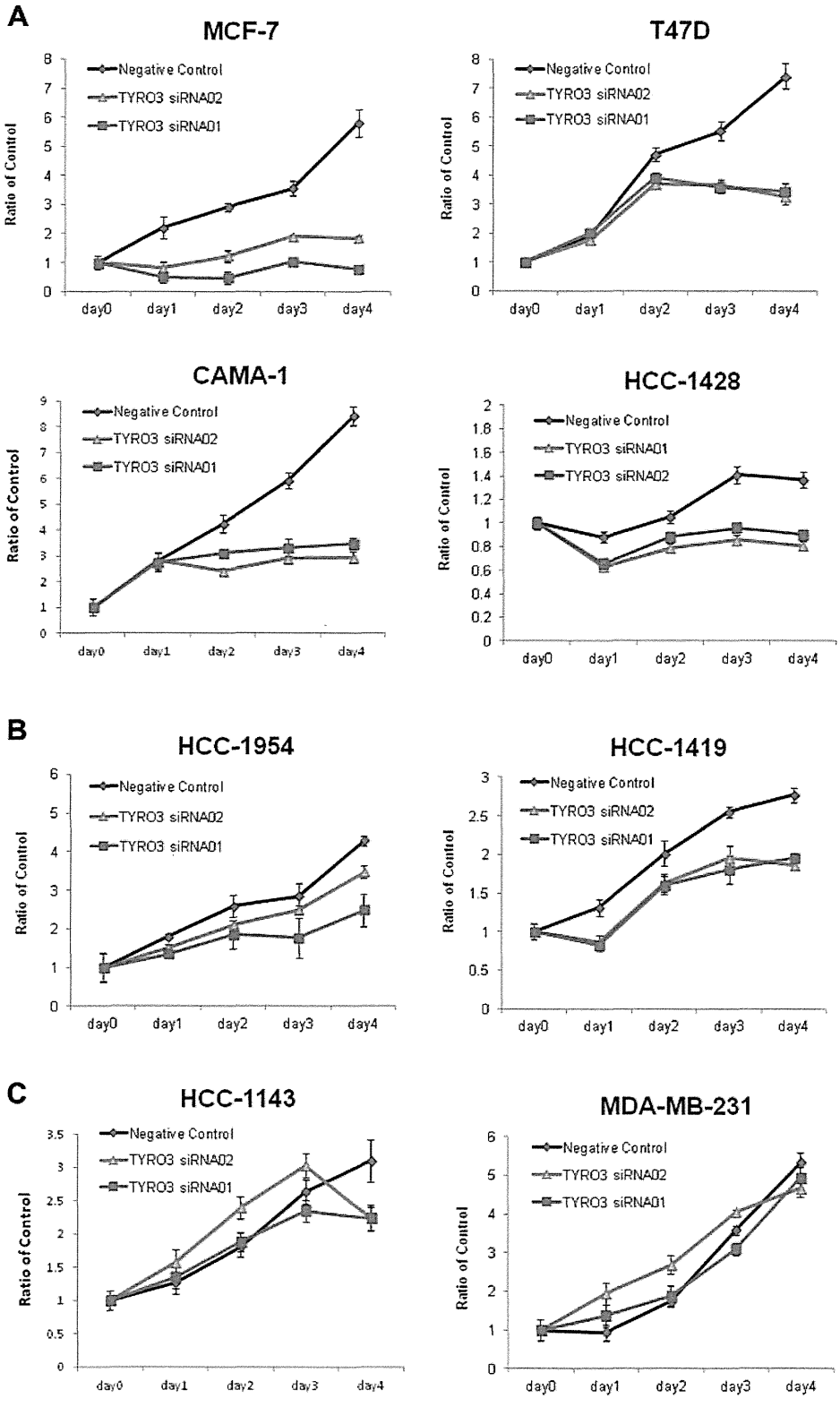

Figure 1. *Impact of TYRO3 gene silencing on cell proliferation. Luminal-type (A), HER2-type (B), and TN-type (C) breast cancer cells were transfected by TYRO3 siRNA clones and negative control siRNA for 24 h. Cells were seeded in 96-well plates and serial growth assays were conducted with MTS assays from day 0 to 4. Daily optical density values shown relative to that of day 0 are shown on the y-axis. Each data point represents the mean value and standard deviation of 6-12 replicate wells.*

fraction along with a decrease in the G_2-M and S fractions, indicating cell-cycle arrest at the G_0-G_1/S boundary, was observed only in luminal- and HER2-type cell lines (Figure 3A and B). In contrast, treatments with TYRO3 siRNA clone 1 and 2 led to little change or rather decreased the G_0-G_1 fraction, respectively, in TN-type cells (Figure 3B). These findings indicated that proliferation inhibition by TYRO3-knockdown was attributable to G_0-G_1/S cell-cycle arrest.

Effect of TYRO3 knockdown on cell signaling. To explore the underlying mechanism of differential cellular responses induced by TYRO3 knockdown, we examined the downstream signaling events of TYRO3 by western blotting. In all cell lines tested, successful TYRO3 knockdown was obtained by two different siRNA clones (Figure 4A-C). In all TYRO3 siRNA-sensitive luminal- and HER2-type cell lines except HCC-1954, TYRO3 siRNAs induced down-regulation of ERK1/2 phosphorylation (Figure 4A and B). In HCC-1954, reduction in the phosphorylation of STAT3 was exclusively accompanied with that in TYRO3 (Figure 4B). In two luminal-type cell lines, decreases in cyclin D1 were also observed following treatment with TYRO3 siRNAs (Figure 4A). In contrast, no consistent change in the phosphorylation of downstream signaling molecules or cyclin D1 expression was observed in either TN-type cell line treated with TYRO3 siRNAs (Figure 4C).

E2 Does not decrease TYRO3 siRNA sensitivity. Because we found the most promising proliferation inhibition after TYRO3 knockdown in luminal-type (ER-positive) cell lines, we decided to evaluate if cellular responses were affected by the level of co-existing E2. Cells were transfected with TYRO3 siRNA in the absence and presence of 10 nM of E2 with or without 1 μM fulvestrant, a selective ER degrader. Results from a proliferation assay showed that in all luminal-type (ER-positive) cell lines, proliferation was promoted in the E2-rich conditions compared to the E2-null conditions when treated with negative control siRNA (Figure 5A). However, the effect of E2 was negated with fulvestrant co-treatment (Figure 5A). In these luminal-type cell lines, TYRO3 siRNA inhibited cell proliferation regardless of the presence or absence of E2 or fulvestrant, suggesting that the effect of TYRO3 siRNA inhibition was independent from the estrogen system (Figure 5A). Conversely, as expected, the same treatments resulted in little change in cell proliferation in TN-type lines (Figure 5B).

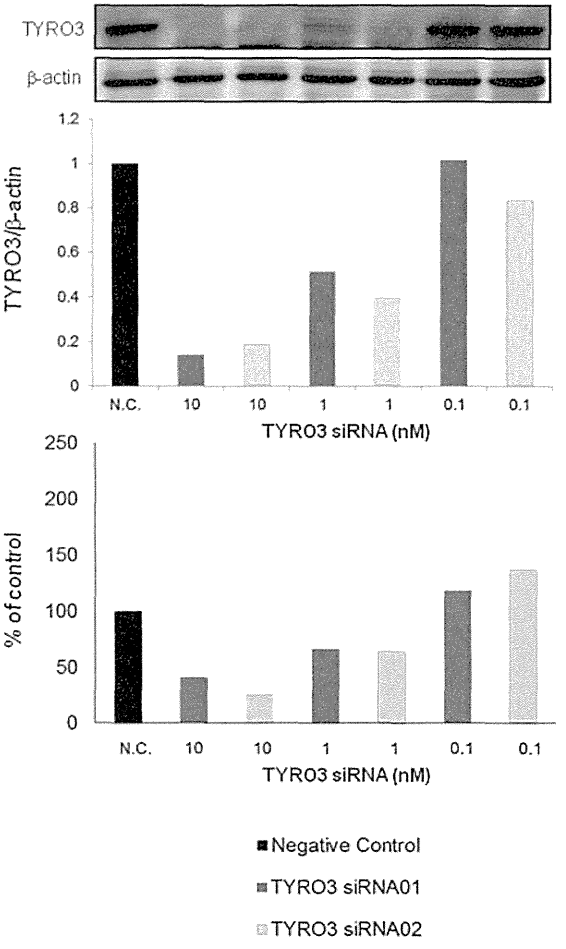

Figure 2. *Correlation between TYRO3 knockdown and proliferation inhibition after siRNA transfection. T47D (luminal-type) cells were treated with different concentrations of each TYRO3 siRNA clone or negative-control siRNA for 24 h. Cells were then plated in 6-cm plates for western blotting and in 96-well plates for proliferation assays. After 72 h of siRNA transfection, TYRO3 protein expression levels were analyzed by western blotting and immunoblots were quantified by densitometry (upper panel); y-axis, TYRO3/β-actin as the average of the ratio to negative control. At the same time point, cells were subjected to MTS assays (lower panel). Optical density values are shown relative to that of the negative control siRNA and each data point represents the mean value and standard deviation of six replicate wells.*

Discussion

In the present study, we revealed the potential therapeutic contribution of TYRO3 inhibition in breast cancer cell lines. TYRO3 knockdown by siRNA induced the most prominent proliferation suppression in luminal-type cells, and to a lesser extent in HER2-type cells, but not in TN-type cells. This inhibitory effect was associated with G_0-G_1/S cell-cycle arrest and inhibition of intracellular signaling.

The role of TYRO3 as a therapeutic target has not previously been evaluated in detail. A recent study showed that nearly all melanoma cell lines tested overexpressed TYRO3, and knockdown of TYRO3 by short hairpin (sh)RNA led to significant cell proliferation inhibition (2), similar to our study. However, while in our study of breast cancer, proliferation inhibition appeared to be due to G_0-G_1/S cell-cycle arrest, in

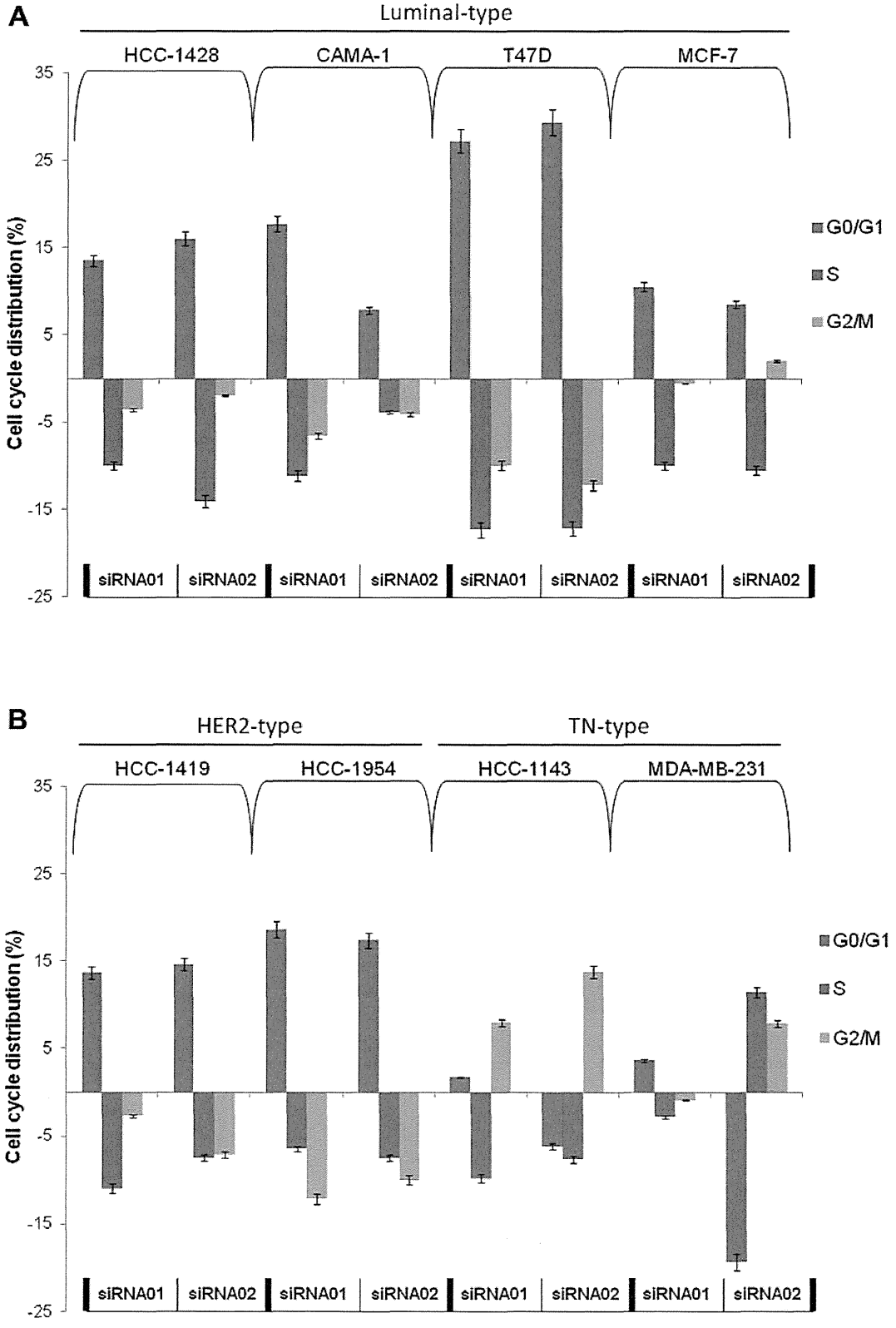

Figure 3. *Changes in cell-cycle distribution following treatment with TYRO3 siRNA. After 72 h of TYRO3 or negative-control siRNA transfection, cell-cycle distribution was assayed. Columns and bars represent absolute changes compared to negative control in each cell-cycle phase and standard deviations, respectively.*

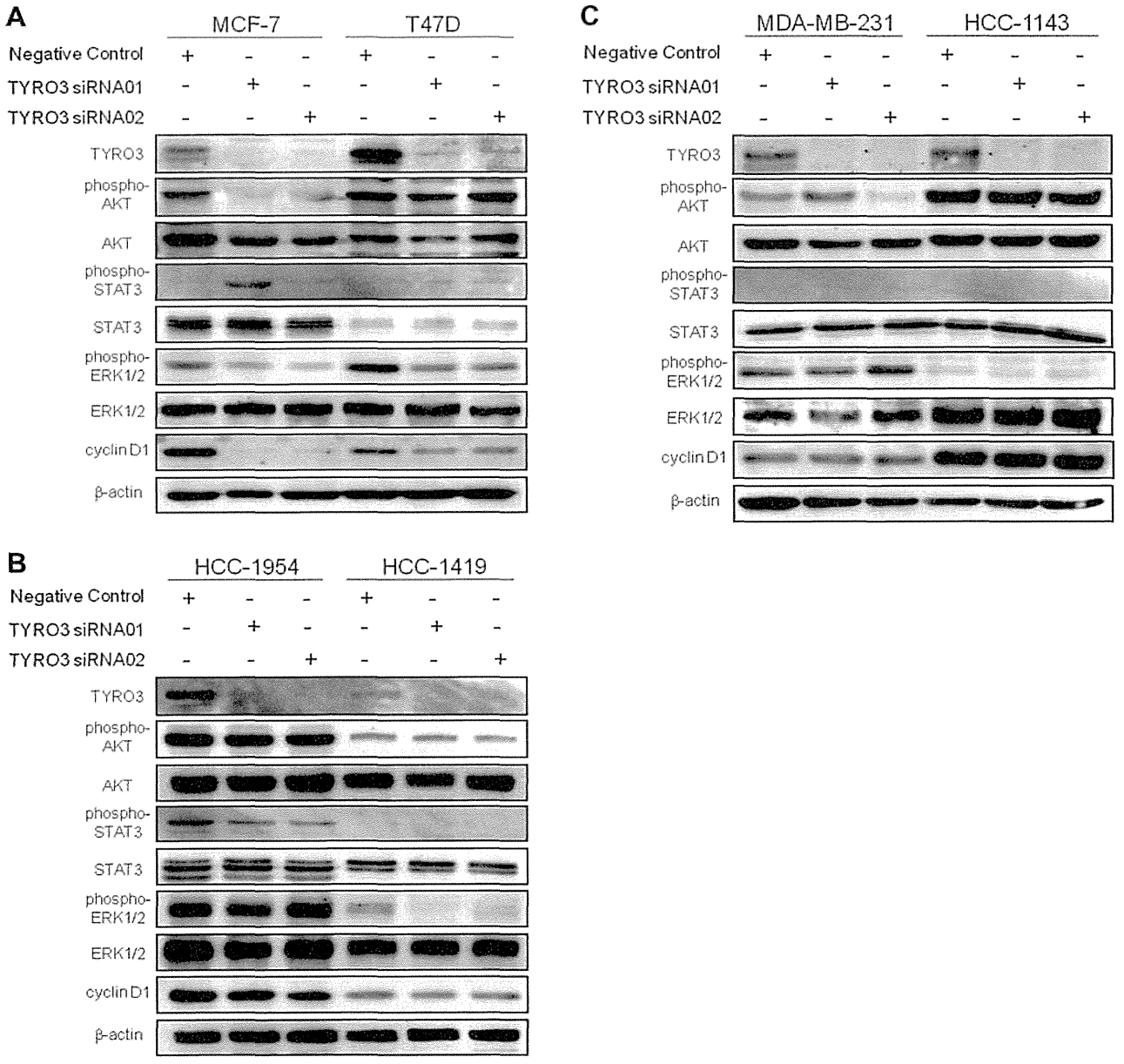

Figure 4. *Effects of TYRO3 knockdown on phosphorylation of downstream signaling molecules. Cellular protein extracts were obtained after 72 h of siRNA transfection. The extracts were subjected to separation on SDS gels followed by immunoblotting for each protein. Blots were stripped and re-probed for β-actin, used as a loading control.*

the melanoma study TYRO3 shRNA alone induced apoptosis (2). It is unknown at this point what determines cellular fate after TYRO3 knockdown.

On developing new targeted-therapies, co-development of pharmacodynamic and response-predictive markers is critical. In our current study, proliferation inhibition by TYRO3 knockdown was associated with reduced phosphorylation of ERK1/2 in three out of four cell lines sensitive to TYRO3 siRNA (Figure 4A and B). Therefore, down-regulation of the phospho-ERK1/2 could be a pharmacodynamic marker. As for response-predictive markers, we investigated several candidates. The first was an intrinsic subtype of breast cancer that is widely used in the clinic; all luminal-type cell lines tested were sensitive to TYRO3 siRNA (Figure 1). The second was the TYRO3 expression level, but it could not be correlated with

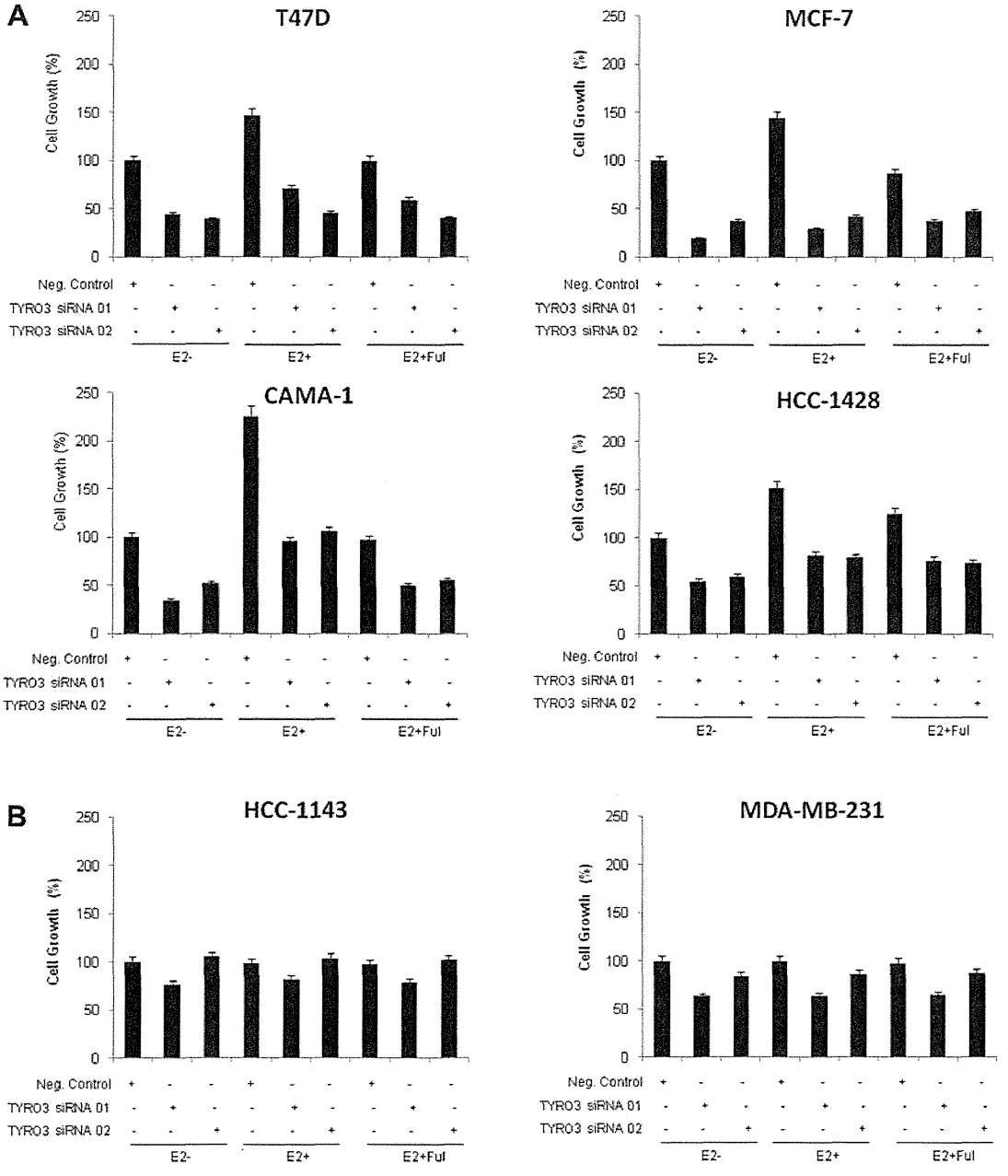

Figure 5. *Effects of E2 on sensitivity to TYRO3 knockdown. Luminal-type (A), and TN-type (B) breast cancer cells were transfected with TYRO3 siRNA clones and negative control siRNA for 24 h and seeded in 96-well plates. Then, 1 μM of fulvestrant and/or 10 nM 17β-E2 were applied for 72 h, and cells were subjected to MTS assays. Optical density values are shown relative to that of the negative control siRNA without E2 and each data point represents the mean value (column) and standard deviation (bar) of six replicate wells.*

sensitivity to TYRO3 knockdown (Figure 4). This finding matched with the above-mentioned study of TYRO3 in melanoma, proving non-correlation between the level of TYRO3 expression and that of sensitivity to TYRO3 shRNA (2). Conversely, phosphorylation of TYRO3 was detectable in only three out of four luminal-type cell lines that were most sensitive to TYRO3 siRNA (Figure 1A and 6), which indicates its potential as a response-predictive marker, albeit unlikely universal. The third was the TYRO3 ligand GAS6; this ligand has been reported to be involved in oncogenic properties such as proliferation (12) and anti-apoptosis (12, 16) specifically in thyroid cancer (1),

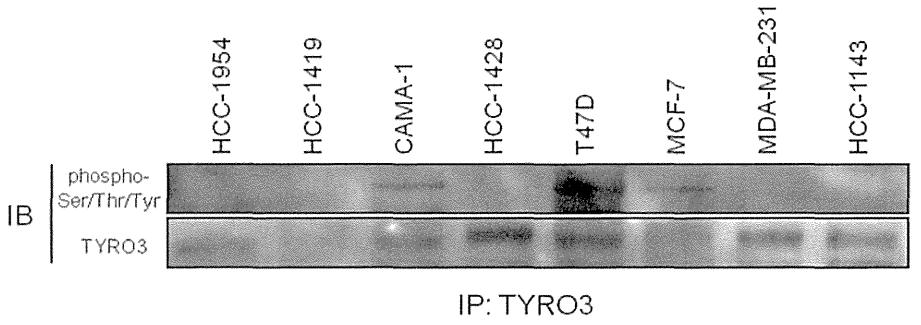

Figure 6. *Phosphorylation of TYRO3 may predict sensitivity to TYRO3 inhibition. Protein extracts (1,500 μg) were immunoprecipitated with an anti-TYRO3 antibody and subjected to immunoblot assays with an anti-phosphoserine/threonine/tyrosine antibody. Phosphorylation of TYRO3 was detectable only in three luminal-type cell lines that were sensitive to TYRO3 knockdown.*

melanoma (2), and leiomyosarcomas (4). On screening GAS6 in the cell culture media of eight breast cancer cell lines, however, no correlation was observed between the concentration of GAS6 and TYRO3 siRNA sensitivity (data not shown).

Upon observing high sensitivity to TYRO3 knockdown in luminal-type cell lines, we predicted cross-talk between TYRO3 and estrogen systems. However, co-existing E2 levels did not interfere with the sensitivity of TYRO3 siRNA (Figure 5A). Although more extensive signaling analysis is required to fully-understand this issue, determinants for TYRO3 dependency in luminal-type cells may be E2 independent. Considering clinical relevance, TYRO3 inhibition might be effective in luminal-type tumors regardless of the patient's menstruation status.

There exist several limitations to our study. First, we did not investigate other possible tumorigenic properties of TYRO3, such as cellular migration and invasion, or anti-apoptosis (17). Second, we did not test the *in vivo* effects of TYRO3 inhibition. This was partially because no specific TYRO3-targeted drug was available. We have tested several tyrosine kinase inhibitors, including BMS777607 and vandetanib, which had been reported to have inhibitory effects on TYRO3 in cell-free conditions (14), but none of them inhibited the *in vitro* cell proliferation of breast cancer cell lines (data not shown). This failure might be simply due to their lack of activity against TYRO3 expression in the cell, or to complex feedback signals following off-target effects. Therefore, development of specific inhibitors against TYRO3 is necessary. In the above-mentioned melanoma study, the researchers developed three types of monoclonal antibodies against TYRO3, and the antibodies were shown to inhibit GAS6-dependent AKT activation (2).

In conclusion, TYRO3 is a potential therapeutic target in breast cancer, particularly in luminal-type cells. Future development of TYRO3-specific agents and response-predictive markers is required.

Declarations of Interest

The Authors declare that they have no conflicts of interest.

Acknowledgements

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ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Lymph Node Metastasis in T4 Maxillary Sinus Squamous Cell Carcinoma: Incidence and Treatment Outcome

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ABSTRACT

Background. The purpose of this study was to evaluate the incidence of lymph node metastasis among patients with T4 maxillary sinus squamous cell carcinoma (MS-SCC) as well as the delayed metastasis rate and the treatment outcome for untreated N0 neck in patients with T4 MS-SCC.

Methods. Consecutive series of all patients ($n = 128$) with previously untreated T4 maxillary sinus SCC between 2006 and 2007 were obtained from 28 institutions belonging to or cooperating in the Head and Neck Cancer Study Group of the Japan Clinical Oncology Group.

Results. Of the 128 patients, 28 (21.9 %) had lymph node metastasis, and six patients (4.7 %) had distant metastasis at diagnosis. Among the 111 patients who were treated with curative intent, 98 had clinically N0 neck disease and did not receive prophylactic neck irradiation. A total of 11 patients (11.2 %) subsequently developed evidence of lymph node metastasis, of whom eight were among the 83 patients with an N0 neck and had not received elective neck treatment. There were 15 patients who received an elective neck dissection as part of the initial treatment, of whom three had pathologically positive for lymph node

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metastases. Of 11 patients, six patients with nonlateral retropharyngeal lymph node metastasis without primary or distant disease were successfully salvaged.

Conclusions. This study identified the incidence of lymph node metastasis among patients with T4 MS-SCC as well as the delayed metastasis rate and the treatment outcome for untreated N0 neck in patients with T4 MS-SCC. These results will be of assistance in selecting treatment strategy for T4 MS-SCC in the future.

Maxillary sinus cancer is the most common form is sinonasal cancer. However, the incidence of it has been considered to be decreasing gradually. According to vital statistics obtained from the Ministry of Health, Labour and Welfare, Japan, the number of deaths due to the maxillary sinus cancer was 1051, 643, and 175, in 1971, 1991, and 2011, respectively. Some investigators in Japan consider this decrease to be correlated with the decrease in sinusitis, which is considered to be one of the risk factors of maxillary sinus cancer.

The Japanese head and neck community has been gaining experience in the treatment of patients with maxillary sinus cancer as a result of the many opportunities we have to treat them, and most head and neck surgeons and radiation oncologists in Japan prefer to take a common sense "wait-and-see" approach in the management of patients with clinically negative neck as the incidence of delayed neck metastasis is considered to be low. However, whether clinically negative neck in patients with the maxillary sinus cancer should be irradiated prophylactically or not is controversial in Europe and the United States.[1,2]

In addition, the incidence of neck metastasis in cases of maxillary sinus cancer has not been well defined, although it is currently believed to be low. To help clarify the situation, a multi-institutional joint research program for maxillary sinus cancer was undertaken in Japan.[3] This study was aimed at evaluating the incidence of lymph node metastasis among patients with T4 maxillary sinus squamous cell carcinoma (MS-SCC) as well as the delayed metastasis rate and the treatment outcome for untreated N0 neck in patients with T4 MS-SCC.

MATERIALS AND METHODS

Consecutive series of all patients with previously untreated T4 MS-SCC between January 2006 and December 2007 were obtained from 28 institutions belonging to or cooperating in the Head and Neck Cancer Study Group of the Japan Clinical Oncology Group. This study was a retrospective analysis. Therefore, the selection criteria for therapeutic modality were decided according to the policy of each institution or individual patient preference. This multi-institutional joint research has been representatively approved by the appropriate ethical committee in the National Hospital Organization Tokyo Medical Center, Tokyo, Japan.

Initial Treatment of the Primary Tumor

The initial therapeutic strategy was classified in the treatment for primary tumor. Surgical treatment was classified into total maxillectomy and partial maxillectomy. The classification of total maxillectomy included extended total maxillectomy with simultaneous orbital exenteration and skull base surgery. "Trimodality therapy," consisting of partial maxillectomy, intra-arterial chemotherapy and radiotherapy, was classified as partial maxillectomy. Surgery in which the anterior wall of the maxillary sinus was opened and the necrotic tumor tissue therein was curetted was also classified as partial maxillectomy. The superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy was defined as RADPLAT, while intravenous chemotherapy with concomitant radiotherapy was defined as IV-CRT. All patients undergoing any form of surgical intervention as part of the initial treatment were classified into either the total or partial maxillectomy group, even if radiotherapy and/or chemotherapy was performed as presurgical or postsurgical therapy. No patients with clinically N0 received elective radiation therapy to the neck lymph nodes.

Local Extension Sites

In this study, the anatomical sites in which the primary tumor had developed were evaluated in detail using CT and/or MR imaging. The local extension sites were classified according to the seventh edition of the Union for International Cancer Control staging system (Table 1). As only two cases had invasion into the brain, with both involving the dura, they were included as extension into the dura/brain. No cases showed involvement of the clivus.

Statistical Analysis

The median follow-up period for the survivors was 4.3 years (range 0.2–5.9 years). Correlations between neck metastasis and variables including age, sex, T-stage, tumor differentiation, and local extension site were tested using Pearson's Chi-square test or Fisher exact test using JMP Pro 10.0.0 statistical software (SAS Institute, Cary, NC, USA). A two-tailed p value <0.05 was considered to be statistically significant.

TABLE 1 Local extension sites

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

RESULTS

A total of 128 patients enrolled. T and N classifications of the 128 patients are shown in Table 2. There were 96 male patients and 32 female. The median age was 64 years (range 30–84 years). A total of 77 patients (60.1 %) had T4a disease, and 51 (39.8 %) had T4b disease. Also, 28 patients (21.9 %) had lymph node metastasis and six patients (4.7 %) had distant metastasis at diagnosis. The distribution of clinically diagnosed lymph node metastasis is shown in Fig. 1. All patients showed clinically N positive, but 1 patient had ipsilateral level Ib or II metastasis. There was one patient with a solitary metastasis in his contralateral level II node. Apart from this patient, all patients with metastasis to other sites had level Ib and/or II metastasis. Regarding correlations between neck metastasis and variables such as age, sex, T stage, tumor differentiation, and local extension site at diagnosis, the nasopharynx ($p = 0.046$) and the hard palate ($p < 0.001$) were the only sites that were correlated with neck lymph node metastasis.

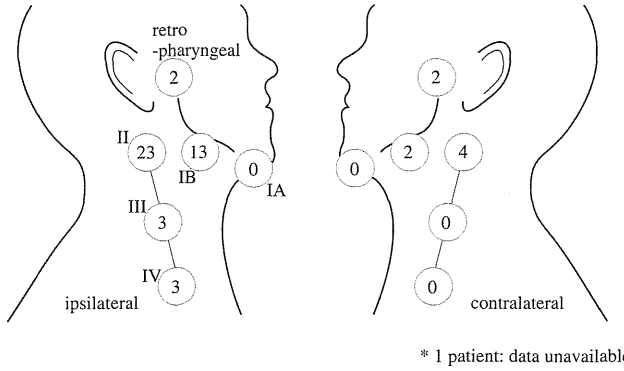
Of the 128 patients, six patients underwent palliative therapy because of distant metastasis. There were three patients who chose to be treated at other institutions, and one patient refused any therapy. The initial treatment for the remaining 118 patients was classified by treatment for primary tumor. A total of 39 of the 118 patients (33 %) were categorized into the total maxillectomy group, while 25 patients (21 %) underwent partial maxillectomy, 22 patients (19 %) underwent RADPLAT, 19 patients (16 %) underwent IV-CRT, and 13 patients (11 %) underwent other therapies, such as radiation alone.

Among the 111 patients who were treated with curative intent, 98 had clinically N0 neck disease and did not receive prophylactic neck irradiation (Fig. 2). A total of 11 patients (11.2 %) subsequently developed evidence of lymph node metastasis, of whom eight were among the 83 patients with an N0 neck and had not received elective

TABLE 2 T and N classification ($n = 128$)

T classification	Number of patients by N classification						Total
	0	1	2a	2b	2c	3	
T4a	62	2 (1)	1	10 (1)	2	0	77 (2)
T4b	38 (1)	5 (1)	0	3	4 (1)	1 (1)	51 (4)
Total	100 (1)	7 (2)	1	13 (1)	6 (1)	1(1)	128 (6)

Number of distant metastasis are shown in parentheses



* 1 patient: data unavailable

FIG. 1 Nodal distribution at diagnosis ($n = 28$)

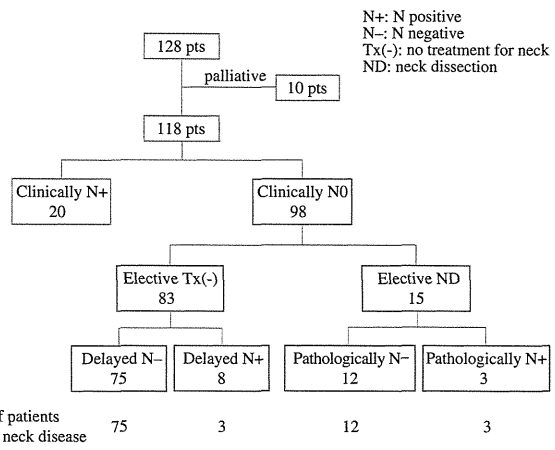


FIG. 2 Clinical course in 98 patients with clinically N0 neck disease

neck treatment. There were 15 patients who received an elective neck dissection as part of the initial treatment, of whom three had tested pathologically positive for lymph node metastases. Delayed neck recurrence was observed at a median 6 months (average, 10 months; range 1–39 months) after the completion of RADPLAT.

Among the eight patients who had no elective neck treatment and developed delayed neck metastasis, three patients were successfully salvaged by neck dissection. However, neck disease could not be controlled in two patients with lateral retropharyngeal lymph node (RPLN) metastasis and three patients with residual or recurrence of primary or distant disease. Neck disease was successfully controlled in 3 patients who had tested pathologically positive for lymph node metastasis after elective neck dissection.

A total of 63 patients with N0 neck disease at diagnosis and who were monitored for neck disease for more than 2 years were analyzed for late neck metastasis. Of the initial 128 patients, 28 patients with clinical neck metastasis at diagnosis, 35 patients with N0 neck disease at diagnosis who died within 2 years due to primary and/or distant disease without neck recurrence, and two patients who died of other causes without neck recurrence were excluded. Of the remaining 63 patients, 11 (17.5 %) had late neck metastasis, as mentioned previously. With regard to correlations between delayed neck metastasis and variables such as age, sex, T stage, tumor differentiation, and local extension sites among the 63 patients, no factor was found to be correlated with neck lymph node metastasis. Moreover, the factors related to a delayed neck metastasis rate of more than 25 % were female gender (4 of 16 = 25 %), T4b (6 of 23 = 26.1 %), low-grade tumor (6 of 17 = 35.3 %), nasopharyngeal invasion (2 of 5 = 40 %), middle cranial fossa invasion (3 of 10 = 30 %), and invasion of a cranial nerve other than V2 (2 of 4 = 50 %).

DISCUSSION

The prognosis for MS-SCC is significantly related to local tumor control. Therefore, lymph node metastasis in MS-SCC has received little attention to date. The incidence and distribution of lymph node metastasis and the percentage of delayed metastasis in cases of maxillary sinus SCC are reported to range widely (Table 3) as MS-SCC is a rare neoplasm and the number of patients treated at a single center is small.[4–9] In addition, some reports have included patients from several decades ago. Time factor must have influence on pretreatment diagnosis and treatment outcome.

The retrospective data in this study were limited to patients with T4 MS-SCC who were treated between 2006 and 2007. Thus, the cases represent a very limited stage treated within a limited period, affording homogeneity to the data. The modality for diagnosis was not checked, but most of the patients were examined by physical examination as well as CT scan and/or MRI at that time. FDG-PET, ultrasound, and fine needle aspiration cytology were used at the attending physician's discretion.

Regarding the correlation between local extension site and neck lymph node metastasis at diagnosis, the nasopharynx and hard palate were both correlated with lymph node metastasis. There was a report that the rate of neck metastasis is much higher in T2 tumors than in T3 or T4 tumors.[10] The reason for this was suspected to be that cases with extension to the hard palate diagnosed as T2 are more likely to develop lymph node metastasis. This study supports this speculation. Cases with invasion to areas known to be rich in lymphatics, such as the nasopharynx and hard palate, are considered more likely to develop lymph node metastasis.[11]

The risk of RPLN metastasis in cases of MS-SCC has been discussed previously.[1,12,13] In 1993, in a series of 25 patients with maxillary sinus cancer, Watarai et al. found

TABLE 3 Incidence of lymph node metastases in patients with MS-SCC reported in the literature

First author	Period	No. of patients	Lymph node metastasis at diagnosis	Delayed lymph node metastasis	Total lymph node metastasis	Institution
Jiang et al.[4]	1969–1985	36	5 (13.8 %)	6 (19.3 %)	11 (30.6 %)	M.D. Anderson Cancer Center
Paulino et al.[5]	1971–1995	42	4 (9.5 %)	11 (28.9 %)	15 (35.7 %)	Loyola University Medical Center
Kim et al.[6]	1984–1993	116	12 (10.3 %)	14 (13.5 %)	26 (22.4 %)	Yonsei Cancer Center, Seoul
Le et al.[7]	1959–1996	58	9 (15.5 %)	6 (12.2 %)	15 (25.9 %)	Stanford University and University of California
Yagi et al.[8]	1982–1997	104	9 (8.6 %)	7 (7.4 %)	16 (15.3 %)	Hokkaido University
Hinerman et al.[9]	1969–2006	54	9 (16.6 %)	3 (6.7 %)	12 (22.2 %)	University of Florida
Present series	2006–2007	128	28 (21.9 %)	11 (11.2 %)	39 (30.5 %)	Japan Clinical Oncology Group

that RPLNs were involved in 16 % of the patients.[12] In this study, only three patients had RPLN metastasis at diagnosis (one patient had bilateral RPLN metastasis) (Fig. 1). Also, two patients who received en bloc tumor resection and radiotherapy as an initial treatment showed delayed RPLN metastasis. The incidence of delayed RPLN metastasis is considered to be low. Therefore, whether the radiotherapy plan should include the RPLN area or not needs to be discussed carefully.

Delayed neck metastasis developed in 11 patients with clinically N0. The possibility of delayed neck metastasis was calculated to be 11.2 %, based on the 98 patients with clinically N0 neck disease among the 118 patients treated with curative intent. This result was comparable with those of previous reports.[4–9] In addition, the delayed neck metastasis rate was 17.5 %, based on the 63 patients with N0 neck disease at diagnosis who were monitored for neck disease for more than 2 years.

The reason why elective neck irradiation was not done for patients with clinically N0 neck in this retrospective multi-institutional study was that we could identify neck metastasis at an early stage and control it effectively as patients were followed up closely. Indeed, all three patients with non-RPLN delayed neck metastasis without residual or recurrent primary or distant disease were successfully salvaged.

Delayed neck metastasis is an unfavorable prognostic factor; therefore, some investigators have recommended prophylactic neck irradiation.[5,7,9,14] In general, elective treatment of the neck is recommended for patients with squamous cell carcinoma of the upper aerodigestive tract when the anticipated risk of occult metastasis is greater than 15–20 %.[15,16] According to this idea, patients with T4N0 MS-SCC should be candidates for elective neck irradiation. However, if close follow-up is possible, we consider that prophylactic neck irradiation is unnecessary, particularly because of the risk of adverse effects of elective neck irradiation, such as mucositis and osteoradionecrosis of the mandible.

In conclusion, this study revealed the incidence of lymph node metastasis among patients with T4 MS-SCC as well as the proportion of cases with delayed metastasis and the treatment outcome for untreated N0 neck disease in patients with T4 MS-SCC. We expect these results to be of assistance in selecting treatment strategies for T4 MS-SCC in the future.

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Measuring quality of life in patients with head and neck cancer: Update of the EORTC QLQ-H&N Module, Phase III

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ABSTRACT: *Background.* The objective of this study was to pilot test an updated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N60).

Methods. Patients with head and neck cancer were asked to complete a list of 60 head and neck cancer-specific items comprising the updated EORTC head and neck module and the core questionnaire EORTC QLQ-C30. Debriefing interviews were conducted to identify any irrelevant items and confusing or upsetting wording.

Results. Interviews were performed with 330 patients from 17 countries, representing different head and neck cancer sites and treatments. Forty-one of the 60 items were retained according to the predefined EORTC criteria for module development, for another 2 items the wording was refined, and 17 items were removed.

Conclusion. The preliminary EORTC QLQ-H&N43 can now be used in academic research. Psychometrics will be tested in a larger field study.
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KEY WORDS: head and neck neoplasms, larynx, pharynx, oral cavity, multimodal therapies, chemoradiation, quality of life

INTRODUCTION

Over the past 30 years, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group (QLG) has developed numerous self-reported questionnaires to assess quality of life (QOL) in oncology.[1] These tools generally use a modular approach, with a 30-item core questionnaire[2] and additional modules for different cancer sites or treatments covering specific symptoms, treatment side-effects, and functional problems. One of the first site-specific modules was the 37-item head and neck cancer module (EORTC QLQ-H&N37), published in 1992.[3] It was subsequently shortened into the QLQ-H&N35 and validated[4] and finally tested in a European field study.[5] Since that time, numerous researchers and clinicians have used the QLQ-

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H&N35, and it has been administered in at least 19 different languages in 26 countries,[6] 8 phase III trials, 10 phase II trials, 42 cohort studies, 2 case-control studies, and 72 cross-sectional studies.[6]

A recent systematic review demonstrated that the QLQ-H&N35 scales possessed robust psychometric characteristics and that it has achieved good acceptance by patients throughout the world.[6] It also revealed, however, that some methodological improvements had been suggested by the users of the QLQ-H&N35, for example, to reduce the relatively high percentage of missing values on the speech (7%) and sexuality (11.5%) scale, or to improve the internal consistency of the speech scale,[6] indicating a need for updating and revising the module. In addition, standard treatments of head and neck cancer have evolved during the past decades, now including induction or simultaneous concomitant chemotherapy and/or targeted therapies more frequently, and it was considered that the H&N35 did not sufficiently cover the side-effects of these treatments.[7,8]

As a consequence, the EORTC Quality of Life Group together with the EORTC Head and Neck Cancer Group including the principal investigator of the QLQ-H&N35 discussed whether or not to revise the QLQ-H&N35. On the one hand, it would be desirable to have a module sensitive to detect QOL issues of current therapy regimens. On the other hand, changing a well-established and widespread questionnaire has the disadvantage that comparisons between studies using different versions would be hindered. Moreover, investigators and clinicians may be in doubt about which version to use in new studies.

Therefore, it was decided to first systematically investigate whether an update of the QLQ-H&N35 was indeed really necessary. After a literature review identifying potentially relevant new issues, we conducted interviews with 137 patients and 96 health care professionals finding that 26 issues relevant for patients' QOL were not part of the current head and neck module,[9] for example, rash and neurological problems, yielding a list of 60 issues. This confirmed that an update of the QLQ-H&N35 would be useful, both from a clinical and a research point of view. This was agreed between the EORTC Quality of Life Group and the EORTC Head and Neck Cancer Group.

Consequently, the new issues were reformatted into items and the EORTC item bank[10] was consulted for consistency. The response format conforms with the EORTC recommendations ranging from 1 = not at all to 4 = very much. The resulting provisional updated module QLQ-H&N60 then needed pilot-testing with respect to understanding, comprehensiveness, and applicability (phase III according to the EORTC Module Development Guidelines),[11] which was the primary purpose of the current study. A secondary purpose was to condense/shorten the module as much as possible without compromising its validity and comprehensiveness.

MATERIALS AND METHODS

Translations

The items were translated from English into Danish, Dutch, French, German, Greek, Hebrew, Italian, Japanese, Mandarin, Norwegian, Polish, Portuguese, Spanish, and Swedish following a standardized forward-backward procedure.[11] After the translation report was approved by the Translation Unit of the EORTC Quality of Life Department, and after native speakers with a clinical background had checked the translation, data collection commenced.

Data collection

Patients were enrolled from 21 collaborating hospitals via members of the EORTC QLG. Patients with head and neck cancer with disease affecting the following tumor sites were eligible: larynx, hypopharynx, nasopharynx, oropharynx, parotid gland, nose, and oral cavity. Exclusion criteria included thyroid and eye cancer, insufficient command of any of the languages that the H&N60 was translated into, and severe cognitive dysfunction. Patients could have had any of the following treatments: surgery alone, surgery with radiotherapy, surgery with (radio) chemotherapy, (radio) chemotherapy alone, radiation alone, and biological therapy with and without any other treatment. Patients could be on or off treatment.

The procedure for patient interviews followed the EORTC QLG Module Development Guidelines.[11] Eligible patients were approached and invited to participate in this study. They received information about this project and could ask the study personnel any questions about the study. Once they had provided written informed consent, they were asked to complete the core questionnaire QLQ-C30 and the updated provisional head and neck module QLQ-H&N60.

After the patient had completed the questionnaire, a brief structured interview was conducted asking if there were any questions that were difficult to understand or perceived as upsetting. If patients found an item difficult to understand or confusing, they were asked to indicate how they would word this question. The interview ended with gaining their opinions on which were the 15 most relevant items, any irrelevant items, and any important items that were not included yet, addressing the entire questionnaire. Questionnaire completion and interview were conducted within one single patient visit.

Data on age, sex, education, tumor site, stage of disease, treatment, and performance status was collected using a Case Report Form to be completed by the interviewer. Data entry was done manually in Leipzig, Germany.

The study protocol was approved by the local ethical committees according to the national requirements. Informed consent was obtained before administration of the provisional module and interviews. Questionnaires were mailed to Leipzig, with no personal identifiable information.

Data analysis

Data analysis was performed in accordance with the EORTC QLG Module Development Guidelines.[11] To retain an item in the module, it should fulfil certain predefined criteria.

Criterion 1, relevance

The item mean value is >1.5 (on a scale of 1–4).

Criterion 2, relevance

More than 50% of the patients rate this item as 3 ("quite a bit") or 4 ("very much").

TABLE 1. Demographic characteristics of the sample ($n = 330$).

Category	No. of patients	(%)
Sex		
Female	92	(27.9)
Male	232	(70.3)
Unknown	6	(1.8)
Age, y		
<50	39	(11.8)
50–59	96	(29.1)
60–69	115	(34.9)
70–79	61	(18.5)
≤80	15	(4.6)
Unknown	4	(1.2)
School education		
Compulsory school education or less	133	(40.3)
Post compulsory school education	117	(35.5)
University level	77	(23.3)
Not specified	3	(0.9)
Country		
Chile	9	(2.7)
Denmark	8	(2.4)
France	13	(3.9)
Greece	9	(2.7)
Germany	66	(20.0)
Israel	22	(6.7)
Italy	37	(11.2)
Japan	5	(1.5)
Norway	25	(7.6)
Poland	13	(3.9)
Portugal	20	(6.1)
Spain	15	(4.6)
Sweden	25	(7.6)
Taiwan	18	(5.5)
The Netherlands	19	(5.8)
United Kingdom	11	(3.3)
United States	15	(4.6)

Criterion 3, neither floor nor ceiling effects

More than 10% of the patients rate this item with a score of 1 or 2; >10% rate this item as 3 or 4.

Criterion 4, range

The responses to the item include the full range of the scale from 1 to 4.

Criterion 5, not upsetting

Less than 5% of the patients find the item upsetting.

Criterion 6, not difficult

Less than 5% of the patients find the item difficult to understand.

Criterion 7, compliance

More than 95% of the patients complete the item.

Criterion 8, priority

More than 10% of the patients rate the item as relevant.

The aim was to include items fulfilling 5 of the first 7 criteria or criterion 8. Additional items could be added if the particular issue was mentioned by at least 5 patients.

Also, items were added to scales according to a hypothesized scale structure and the internal consistency (Cronbach's Alpha) of this scale was calculated. This information was used as an additional "Criterion α" indicating that the item can meaningfully be combined with other items to form a multi-item scale (ie, Cronbach's Alpha is ≥0.70) and the Alpha decreases if the item is removed.

All these criteria were tabulated together with the results of the methodological review[6] and the results discussed with a multiprofessional expert group at the EORTC QLG Spring Meeting 2013. This group decided, based on the results, their clinical experience, and the results of the review,[6] whether to keep the item as is, to remove the item, or change the wording.

RESULTS

Sample

Between August 2011 and February 2013, a total of 333 patients were enrolled. Three patients were excluded because they had thyroid ($n = 1$) or eye cancer ($n = 2$), resulting in 330 eligible participants. Patients came from 21 institutions in 17 countries, distributed over Central Europe ($n = 66$), Southern Europe ($n = 81$), Northern Europe ($n = 58$), Eastern Europe ($n = 13$), Western Europe ($n = 43$), Asia ($n = 45$), Northern America ($n = 15$), and Southern America ($n = 9$). Seventy percent of the patients were men, and the average age was 61 years (range, 25–89 years). The most frequent tumor site was oral cavity ($n = 94$), followed by oropharynx ($n = 80$), and larynx ($n = 79$). Full demographic and clinical sample characteristics are shown in Tables 1 and 2.

Module administration

The time needed to complete the H&N60 was less than 10 minutes in 30% of all cases, 41% needed 11 to 15 minutes, 18% needed 16 to 20 minutes, 8% needed 21 to 30 minutes, and 3% needed more than 30 minutes.

Sixty-eight percent completed the module on their own, 25% needed assistance from the interviewer, and 7% from relatives or friends.

Preliminary module

Based on the predefined thresholds, 47 of the 60 items had a mean >1.5 and therefore fulfilled criterion 1, none had >50% responses of "quite a lot" or "very much" (criterion 2), 55 had neither floor nor ceiling effects (criterion 3), all had a range of 1 to 4 (criterion 4), 58 were not upsetting for more than 5% (criterion 5), 58 were not difficult to understand for more than 5% (criterion 6), and 56 were completed by >95% of the patients (criterion 7). Fifty-two items fulfilled at least 5 of these 7 criteria. Fifteen items were prioritized by >10% of the patients (criterion 8). All of the highly prioritized items fulfilled at least 5 of the first 7 criteria.

Considering these criteria and the preliminary scale structure, the expert group decided to retain 41 items as they were, to amend the wording of 2 items, and to remove 17 items. Details are shown in Table 3. The wording of item 46 was changed from "Have you had problems because of losing some teeth (as part of your

TABLE 2. Clinical characteristics of the sample ($n = 330$).

Category	No. of patients	(%)
Tumor site		
Larynx	79	(23.9)
Hypopharynx	19	(5.8)
Oropharynx	80	(24.2)
Nasopharynx	18	(5.5)
Oral cavity	94	(28.5)
Parotid gland	6	(1.8)
Nasal cavity and sinuses	19	(5.8)
Unknown primary	5	(1.5)
Other	8	(2.4)
Unknown	2	(0.6)
Karnofsky performance score		
≤50	7	(2.1)
60	36	(10.9)
70	60	(18.2)
80	66	(20.0)
90	105	(31.8)
100	54	(16.4)
Unknown	2	(0.6)
Recurrent disease		
No	279	(84.6)
Yes	47	(14.2)
Unknown	4	(1.2)
Tumor stage (UICC 2005)		
I	41	(12.4)
II	55	(16.7)
III	62	(18.8)
IV	148	(44.9)
Unknown	24	(7.3)
Treatment		
OP alone	58	(17.6)
RT alone	35	(10.6)
CT alone	6	(1.8)
RCT without OP	67	(20.3)
OP + RCT	77	(23.3)
OP + CT	3	(0.9)
OP + RT	78	(23.6)
Other	3	(0.9)
Unknown	2	(0.6)
Targeted therapy		
No	295	(89.4)
Yes	32	(9.7)
Unknown	3	(0.9)
Stage of treatment		
Before treatment	11	(3.3)
During treatment	132	(40.0)
<6 mo after end of treatment	49	(14.9)
≥6 mo after end of treatment	63	(19.1)
≥12 mo after end of treatment	71	(21.5)
Unknown	4	(1.2)

Abbreviations: UICC, Union for International Cancer Control; OP, surgery; RT, radiotherapy; CT, chemotherapy; RCT, radio-chemotherapy.

treatment)?" into "Have you had problems because of losing some teeth?" and item 71 from "Have you been hoarse?" into "Have you had problems with hoarseness?"

There were 44 additional items suggested by patients. The most frequently mentioned issues were doctor-patient-relationship (4×), mental well-being (3×), and information about the disease or treatment (2×). However, none was mentioned 5 times or more. In addition, these issues are covered by the QLQ-C30 and the EORTC information module.[12] Therefore, no new items were added to the questionnaire and the resulting preliminary module contains 43 items.

DISCUSSION

The EORTC QLQ-H&N43 is an updated and revised version of the EORTC QLQ-H&N35, measuring QOL in patients with head and neck malignancies excluding eye and thyroid cancers. Patients representing different tumor sites, tumor stages, treatment options, and treatment phases were included in this update to ensure that the module is applicable in a broad variety of clinical studies.

Traditionally, the EORTC H&N module has followed the concept of targeting a heterogeneous group of patients. This is in contrast to other EORTC QOL modules. For example, the modules for patients with gynecological malignancies were developed separately for cervical,[13] endometrial,[14] and ovarian cancer,[15] and a module for vulval cancer is currently under development. That approach has certain advantages. For example, the module can be shorter as the variety and number of QOL issues relevant to the patients is smaller because the disease and the treatment-specific side effects are similar. Shorter questionnaires are usually preferred by clinicians and researchers. However, as many clinical trials in head and neck oncology enroll patients with different tumor sites, it was decided after discussion within the EORTC Quality of Life Group and the EORTC Head and Neck Cancer Group to continue with the previous concept of having one single module for all types of head and neck malignancies (except eye and thyroid cancer, which are specific entities with their own profile of QOL experience). This ensures that within one trial one module can be used instead of needing to include two or more different modules. As a consequence, the module is somewhat longer than other EORTC questionnaires. Compared to the previous version, QLQ-H&N35, it contains additional questions regarding skin problems, a typical symptom after targeted therapy,[16] neurological side-effects, and shoulder problems, whereas some issues that can be assessed more reliably by other means were removed (for example, weight or pain medication). However, the QLQ-H&N43 contains many scales of the QLQ-H&N35, thus, data from studies using the 2 different versions of the EORTC head and neck module will be comparable to some extent. We also tried to harmonize the QLQ-H&N43 with the newly developed EORTC oral health module OH-17.[17] However, although there are some overlapping issues across both modules, they do not focus on the same QOL areas. The OH-17 targets oral health issues in a variety of cancer diagnoses whereas the head and neck module is for head and neck cancer only.

The patients in our sample can be considered representative of a wider head and neck cancer population. The male/female ratio, as well as the distribution of tumor sites, mirrors the incidence data of head and neck malignancies. The educational level is probably skewed to a higher educational level than the general head and neck cancer population, although we can state that participants

TABLE 3. Results of patient interviews.

					crit α		crit 1		crit 2		crit 3		crit 4		crit 5		crit 6		crit 7				crit 8	
item Nr	wording	hypothesized scale	α of hypothesized scale	α if item removed	decreased α if item removed?	mean	mean > 1.5?	proportion of scores 3/4	scores 3/4 >50%?	proportion of scores 1/2	neither floor nor ceiling	range	range	% upsetting	<5% upsetting	% difficult	<5% difficult	proportion complete	>95% complete?	sum crit 1 to 7	min. 5 of crit 1 to 7?	proportion relevant	>= 10% relevant	Decision
q 31	Have you had a swelling in your neck?	LY	n.a.	n.a.	1	1.7	1	0.20	0	0.79	1	1–4	1	0.00	1	0.00	1	1.00	1	6	1	0.08	0	keep
q 32	Have you had problems with wound healing?	WOU	0.45	n.a.	0	1.4	0	0.14	0	0.84	1	1–4	1	0.00	1	0.01	1	0.98	1	5	1	0.04	0	keep
q 33	Have you had skin problems (e.g. itchy, dry)?	SKIN	0.82	0.75	1	1.8	1	0.23	0	0.77	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.08	0	keep
q 34	Has dryness of your skin bothered you?	SKIN	0.82	0.74	1	1.6	1	0.15	0	0.82	1	1–4	1	0.00	1	0.00	1	0.98	1	6	1	0.06	0	remove
q 35	Have you had tingling or numbness in your hands or feet?	NEU	0.48	n.a.	0	1.5	1	0.14	0	0.86	1	1–4	1	0.00	1	0.00	1	1.00	1	6	1	0.04	0	keep
q 36	Have you felt dizzy?	NEU	0.48	n.a.	0	1.5	0	0.11	0	0.88	1	1–4	1	0.00	1	0.00	1	0.99	1	5	1	0.02	0	remove
q 37	Have you had a rash?	SKIN	0.82	0.82	1	1.3	0	0.07	0	0.91	0	1–4	1	0.00	1	0.00	1	0.98	1	4	0	0.03	0	keep
q 38	Have you had problems with hearing because of your treatment?	HEAR	n.a.	n.a.	1	1.5	0	0.15	0	0.84	1	1–4	1	0.00	1	0.00	1	0.99	1	5	1	0.05	0	remove
q 39	Has your skin colour changed?	SKIN	0.82	0.81	1	1.4	0	0.11	0	0.88	1	1–4	1	0.00	1	0.01	1	0.99	1	5	1	0.04	0	keep
q 40	Have you been bothered by itchy skin?	SKIN	0.82	0.78	1	1.5	0	0.11	0	0.88	1	1–4	1	0.00	1	0.00	1	0.99	1	5	1	0.03	0	remove
q 41	Have you had trouble speaking clearly?	SP	0.84	0.78	1	2.2	1	0.35	0	0.64	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.12	1	keep
q 42	Have you had trouble talking in a noisy environment?	SP	0.84	0.80	1	2.1	1	0.33	0	0.66	1	1–4	1	0.00	1	0.01	1	0.98	1	6	1	0.07	0	keep
q 43	Has it been difficult to raise your arm or to move it sideways?	SHO	0.84	n.a.	1	1.6	1	0.19	0	0.79	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.07	0	keep
q 44	Have you had pain in your shoulder?	SHO	0.84	n.a.	1	1.7	1	0.19	0	0.81	1	1–4	1	0.00	1	0.00	1	1.00	1	6	1	0.04	0	keep
q 45	Have you had problems with transferred tissue (your flap	WOU	0.45	n.a.	0	1.3	0	0.07	0	0.84	0	1–4	1	0.00	1	0.08	0	0.91	0	2	0	0.02	0	remove

TABLE 3. *Continued*

					crit α		crit 1		crit 2		crit 3		crit 4		crit 5		crit 6		crit 7			crit 8		
item Nr	wording	hypothesized scale	α of hypothesized scale	α if item removed	decreased α if item removed?	mean	mean > 1.5?	proportion of scores 3/4	scores 3/4 >50%?	proportion of scores 1/2	neither floor nor ceiling	range	range	% upsetting	<5% upsetting	% difficult	<5% difficult	proportion complete	>95% complete?	sum crit 1 to 7	min. 5 of crit 1 to 7?	proportion relevant	>= 10% relevant	Decision
	put in at your operation)?																							
q 46	Have you had problems because of losing some teeth (as part of your treatment)?	TE	0.78	0.73	1	1.8	1	0.24	0	0.73	1	1–4	1	0.00	1	0.01	1	0.98	1	6	1	0.07	0	change
q 47	Have you had trouble chewing?	TE	0.78	0.70	1	2.2	1	0.37	0	0.61	1	1–4	1	0.00	1	0.01	1	0.98	1	6	1	0.15	1	keep
q 48	Have you felt uncomfortable about being physically intimate?	PC	0.82	0.79	1	1.7	1	0.18	0	0.76	1	1–4	1	0.03	1	0.05	0	0.94	0	4	0	0.04	0	remove
q 49	Have you felt less physically attractive as a result of your disease or treatment?	BI	0.87	0.84	1	1.8	1	0.24	0	0.74	1	1–4	1	0.02	1	0.02	1	0.98	1	6	1	0.05	0	keep
q 50	Have you felt dissatisfied with your body?	BI	0.87	0.84	1	1.7	1	0.18	0	0.80	1	1–4	1	0.01	1	0.02	1	0.98	1	6	1	0.06	0	keep
q 51	Have you felt less feminine/masculine as a result of your illness or treatment?	BI	0.87	0.85	1	1.5	0	0.14	0	0.83	1	1–4	1	0.01	1	0.02	1	0.97	1	5	1	0.05	0	remove
q 52	Have you been worried about your return to work?	ANX	0.77	0.83	0	1.6	1	0.17	0	0.78	1	1–4	1	0.00	1	0.03	1	0.95	1	6	1	0.04	0	remove
q 53	Have you been worried about the results of examinations and tests?	ANX	0.77	0.60	1	2.2	1	0.34	0	0.65	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.12	1	keep
q 54	Have you been worried about your health in the future?	ANX	0.77	0.58	1	2.4	1	0.41	0	0.59	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.16	1	keep
q 55	Have you felt less secure because your look has changed?	BI	0.87	0.85	1	1.6	1	0.17	0	0.82	1	1–4	1	0.01	1	0.00	1	0.98	1	6	1	0.04	0	remove
q 56	Have you had pain in your mouth?*	PA	0.85	0.76	1	1.9	1	0.28	0	0.72	1	1–4	1	0.00	1	0.01	1	1.00	1	6	1	0.15	1	keep

TABLE 3. *Continued*

					crit α		crit 1		crit 2		crit 3	crit 4		crit 5		crit 6		crit 7				crit 8		
item Nr	wording	hypothesized scale	α of hypothesized scale	α if item removed	decreased α if item removed?	mean	mean > 1.5?	proportion of scores 3/4	scores 3/4 >50%?	proportion of scores 1/2	neither floor nor ceiling	range	range	% upsetting	<5% upsetting	% difficult	<5% difficult	proportion complete	>95% complete?	sum crit 1 to 7	min. 5 of crit 1 to 7?	proportion relevant	>= 10% relevant	Decision
q 57	Have you had pain in your jaw? *	PA	0.85	0.82	1	1.6	1	0.20	0	0.79	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.07	0	keep
q 58	Have you had soreness in your mouth? *	PA	0.85	0.77	1	1.9	1	0.24	0	0.74	1	1–4	1	0.00	1	0.00	1	0.98	1	6	1	0.11	1	keep
q 59	Have you had pain in your throat? *	PA	0.85	0.86	0	1.9	1	0.26	0	0.73	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.12	1	keep
q 60	Have you had problems swallowing liquids? *	SW	0.86	0.81	1	1.8	1	0.24	0	0.75	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.12	1	keep
q 61	Have you had problems swallowing pureed food? *	SW	0.86	0.78	1	1.8	1	0.24	0	0.75	1	1–4	1	0.00	1	0.02	1	0.99	1	6	1	0.14	1	keep
q 62	Have you had problems swallowing solid food? *	SW	0.86	0.82	1	2.3	1	0.41	0	0.58	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.20	1	keep
q 63	Have you choked when swallowing? *	SW	0.86	0.88	0	1.7	1	0.18	0	0.81	1	1–4	1	0.00	1	0.02	1	0.99	1	6	1	0.11	1	keep
q 64	Have you had problems with your teeth? *	TE	0.78	0.69	1	1.8	1	0.24	0	0.76	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.07	0	keep
q 65	Have you had problems opening your mouth wide? *	OM	n.a.	n.a.	1	1.9	1	0.29	0	0.70	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.08	0	keep
q 66	Have you had a dry mouth? *	DR	0.78	n.a.	1	2.4	1	0.46	0	0.53	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.16	1	keep
q 67	Have you had sticky saliva? *	DR	0.78	n.a.	1	2.3	1	0.40	0	0.59	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.15	1	keep
q 68	Have you had problems with your sense of smell? *	SE	0.69	n.a.	0	1.7	1	0.24	0	0.75	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.05	0	keep
q 69	Have you had problems with your sense of taste? *	SE	0.69	n.a.	0	2.2	1	0.39	0	0.60	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.12	1	keep
q 70	Have you had problems with coughing? *	CO	n.a.	n.a.	1	1.9	1	0.25	0	0.74	1	1–4	1	0.00	1	0.00	1	1.00	1	6	1	0.05	0	keep
q 71	Have you been hoarse? *	SP	0.84	0.89	0	1.9	1	0.26	0	0.73	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.04	0	change
q 72	Have you felt ill? *	FI	n.a.	n.a.	1	1.8	1	0.24	0	0.75	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.03	0	remove
q 73	Has your appearance bothered you? *	BI	0.87	0.85	1	1.6	1	0.16	0	0.83	1	1–4	1	0.00	1	0.00	1	0.98	1	6	1	0.03	0	keep

TABLE 3. *Continued*

					crit α		crit 1		crit 2		crit 3		crit 4		crit 5		crit 6		crit 7			crit 8		
item Nr	wording	hypothesized scale	α of hypothesized scale	α if item removed	decreased α if item removed?	mean	mean > 1.5?	proportion of scores 3/4	scores 3/4 >50%?	proportion of scores 1/2	neither floor nor ceiling	range	range	% upsetting	<5% upsetting	% difficult	<5% difficult	proportion complete	>95% complete?	sum crit 1 to 7	min. 5 of crit 1 to 7?	proportion relevant	>= 10% relevant	Decision
q 74	Have you had problems eating? *	SO	0.85	0.83	1	2.2	1	0.39	0	0.60	1	1–4	1	0.00	1	0.01	1	0.99	1	6	1	0.13	1	keep
q 75	Have you had problems eating in front of your family? *	SO	0.85	0.81	1	1.6	1	0.18	0	0.80	1	1–4	1	0.00	1	0.02	1	0.98	1	6	1	0.06	0	keep
q 76	Have you had problems eating in front of other people? *	SO	0.85	0.79	1	1.8	1	0.24	0	0.75	1	1–4	1	0.00	1	0.02	1	0.98	1	6	1	0.08	0	keep
q 77	Have you had problems enjoying your meals? *	SO	0.85	0.82	1	2.1	1	0.33	0	0.66	1	1–4	1	0.00	1	0.01	1	0.98	1	6	1	0.11	0	keep
q 78	Have you had problems talking to other people? *	SP	0.84	0.78	1	1.8	1	0.26	0	0.74	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.08	0	keep
q 79	Have you had problems talking on the telephone? *	SP	0.84	0.77	1	1.9	1	0.27	0	0.72	1	1–4	1	0.00	1	0.01	1	0.98	1	6	1	0.09	0	keep
q 80	Have you had problems having social contact with your family or friends? *	SC	0.71	n.a.	1	1.4	0	0.10	0	0.89	0	1–4	1	0.00	1	0.02	1	0.99	1	4	0	0.03	0	remove
q 81	Have you had problems going out in public? *	SC	0.71	n.a.	1	1.5	0	0.14	0	0.84	1	1–4	1	0.00	1	0.01	1	0.98	1	5	1	0.04	0	keep
q 82	Have you had problems having close physical contact with family or friends? *	PC	0.82	0.85	0	1.3	0	0.08	0	0.88	0	1–4	1	0.01	1	0.02	1	0.96	1	4	0	0.02	0	remove
q 83	Have you felt less interest in sex? *	PC	0.82	0.69	1	2.0	1	0.29	0	0.63	1	1–4	1	0.06	0	0.04	1	0.92	0	4	0	0.05	0	keep
q 84	Have you felt less *sexual enjoyment*? *	PC	0.82	0.70	1	1.9	1	0.25	0	0.64	1	1–4	1	0.06	0	0.04	1	0.88	0	4	0	0.03	0	keep
q 85	Have you used pain-killers? *	PK	n.a.	n.a.	1	2.1	1	0.34	0	0.65	1	1–4	1	0.00	1	0.00	1	0.99	1	6	1	0.05	0	remove
q 86	Have you taken any nutritional supplements (excluding vitamins)? *	NU	n.a.	n.a.	1	1.7	1	0.22	0	0.75	1	1–4	1	0.00	1	0.01	1	0.98	1	6	1	0.02	0	remove