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Ultrasound in patients with treated head and neck carcinomas

A retrospective analysis for effectiveness of follow-up care

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Abstract

Correct follow-up is necessary to avoid under- or overtreatment in the care of patients with treated carcinomas of head and neck. Ultrasound is a cost-effective, harmless, easy, and feasible method. It can be applied in the outpatient clinic in follow-up but the United Kingdom National Multidisciplinary guidelines are recommended computed tomography or magnetic resonance imaging for the detection of metastasis for head and neck carcinomas in the follow-up period. The purpose of the study was to state that neck ultrasound would be the method of choice on follow-up care of Chinese patients who received primary treatment for carcinoma of head and neck.

Patients who received primary treatment for carcinoma of the head and neck were examined for 5-years in follow-up through physical, clinical, and neck ultrasound (n = 198). If patients had no evidence of disease after 60 months of definitive therapy considered as a cure. If patients had no evidence of disease after 36 months of salvage therapy considered as a cure of recurrence.

Irrespective of definitive treatment used, the study was monitored through neck ultrasound during 5 years of a follow-up visit and was reported cure in 126 (64%) patients and recurrence in 72 (36%; distant metastasis: 33 [17%], local recurrence: 24 [12%], and regional recurrence: 15 [7%]) patients. Primary tumor stage IV, III, II, and I had 63% (15/24), 51% (21/41), 32% (18/56), and 23% (18/77) recurrence, respectively. The time to detect regional recurrence was shorter than that for local recurrence ($P < .0001$, $q = 15.059$) and distant recurrence ($P < .0001$, $q = 7.958$). Local recurrence and stage I primary tumor had the highest percentage cure for recurrence.

Neck ultrasound in the follow-up period is reported to be effective for the detection of recurrence of patients who received primary treatment for carcinoma of head and neck especially regional recurrence and primary tumor stage I.

Level of Evidence: III.

Abbreviations: ANOVA = analysis of variance, q = critical value, SD = Standard Deviation.

Keywords: head and neck carcinoma, metastasis, neck ultrasound, recurrence, tumor site, tumor stage

1. Introduction

The carcinomas of head and neck disable patients in multiple activities, like respiration, gulp, and conversation, which are connected to an anatomically condensed area. Therefore, early detection of the recurrence of head and neck carcinomas is important. Depending on the location of the recurrence and size of the tumor, patients may be given preventive treatment for therapeutic or palliative purposes. However, tumor enlargement

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The datasets generated during and/or analyzed during the present study are not publicly available, but are available from the corresponding author on reasonable request.

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within a few days would change the treatment strategy and the extent of incision and functional restoration.[1] One of the major goals during the follow-up period after primary treatment for patients with carcinomas of head and neck is the initial investigation of local and regional recurrence(s).[2] Although intensifying monitoring after treatment, significant curative therapy for recurrence of carcinomas of head and neck is not achieved.[3] In most cases, chest x-rays, the computed tomography, and panendoscopy are used for detection of recurrence[4] in the follow-up period every month after definitive treatment. Also, the outcomes of salvage therapy are not satisfactory.[2] United Kingdom National Multidisciplinary guidelines are recommended the computed tomography or magnetic resonance imaging for the detection of recurrence in the follow-up period for carcinomas of head and neck.[5]

Ultrasound is the method of choice for monitoring thyroid tumors and lymphoma; however, for the other head and neck tumors the method of choice is the computed tomography scan and magnetic resonance imaging due to the capacity of bone analysis and of the structures that cause a barrier to the sound wave penetration. Neck ultrasound reported a high sensitivity for re-staging after primary chemoradiotherapy for carcinomas of head and neck.[6] Moreover, ultrasound is cost-effective, harmless, easy, and feasible. It can be applied in the outpatient clinic in the follow-up period.[2] It is reported as a valid method for neck metastasis detection.[7] Three-dimensional Doppler ultrasonography is reported as a reliable method for detecting the recurrence of patients with squamous cell carcinoma of head and neck.[8] However, a retrospective analysis reported no significant importance of neck ultrasound in the detection of recurrence in the patients who received primary treatment for squamous cell carcinoma of head and neck during the follow-up period.[2]

The objective of the retrospective analysis of the cross-sectional study was to state that neck ultrasound would be the method of choice on follow-up care of Chinese patients who received primary treatment for carcinoma of head and neck because it is more affordable and has wider availability in medical centers, which may be devoid of the computed tomography scan and magnetic resonance imaging, was not reached.

2. Materials and methods

2.1. Ethics approval and consent to participate

The designed protocol (GCPH/CL/11/20 dated June 13, 2020) was approved by the Gong'an County People's Hospital human ethics committee and the Chinese Society of Clinical Oncology. An informed consent form was signed by patients or their relative (legally authorized person) for diagnosis during follow-up. Written informed consent was obtained from the patient(s) or their relative (legally authorized person) for patients anonymized information to be published in the article form. Being retrospective study registration in the Chinese clinical trial registry was waived by the local authority.

2.2. Study population

Patients who received definitive treatment (surgery, chemotherapy, and/ or radiotherapy) for head and neck carcinoma of stage I, II, III, and IV and available in the follow-up period for diagnosis and treatment (if required) of January 2014 to June 2020 were retrospectively considered for inclusion in the study.

2.3. Follow-up of patients

Patients were examined every month (for the first year), every second month (for the second year), every third month (for the third year), every fourth month (for the fourth year), every fifth month (for the fifth year), and thereafter at 6-month intervals.

2.4. Follow-up examination

Follow-up examinations were included the clinical history followed by head and neck examinations and neck ultrasound. The chest x-ray was performed at 6-month intervals. If suspected recurrences were reported, endoscopic biopsies following cytopathology were performed under general anesthesia. The computed tomography was also preferred as a choice during follow-up only when significant uncertainties for a neck ultrasound (irrespective of the primary site tumor stage).

2.5. Neck ultrasound

Neck ultrasound (EPIQ Elite, BioSpace, Longmont, CO included gray scale and color duplex scan of neck level regions I to VI using a 7.5 MHz linear array transducer. Ultrasound was performed by ultrasound technologists (a minimum of 3 years of experience in head and neck images) of the institute. The size (short-axis diameter /.0.8 cm), hypoechogenicity (concerning to the surrounding muscles), heterogeneous internal echo, irregular margin, chaotic or absent vascular pattern, and/ or taller than wide shape ($\frac{\text{Short axis}}{\text{Long axis}} > 0.5$) was considered as recurrence.[9] The representative ultrasound images of neck metastasis are demonstrated in Figure 1:

2.6. Cure

If patients had no evidence of disease after 60 months of definitive therapy considered as a cure.

2.7. Salvage therapy

Chemotherapy or chemotherapy plus radiotherapy was preferred for salvage therapy. Surgery was performed if necessary.

2.8. Cure of recurrence

If patients had no evidence of disease after 36 months of salvage therapy considered as a cure of recurrence.

2.9. Statistical analysis

The sample size determined on the basis that the assumption that $30\% \pm 5\%$ patients are reported recurrence, type-II error 20%, type-I error 5%, and 95% level of confidence. The minimum patients required for study (the sample size) was reported 180 (SPSS v25.0 IBM Corporation, Armonk, NYor statistical analysis purposes). One-way analysis of variance (ANOVA) following the Dunnett multiple comparisons test (considering critical value $[q] > 2.266$ as significant) was used for statistical analysis for time for the detection of recurrence for different site metastasis. All results were considered significant if the P value was reported $<.05$.

3. Results

3.1. Study population and characteristics of patients

From January 15, 2014 to February 2, 2015, a total of 198 patients received primary treatment (surgery and chemotherapy

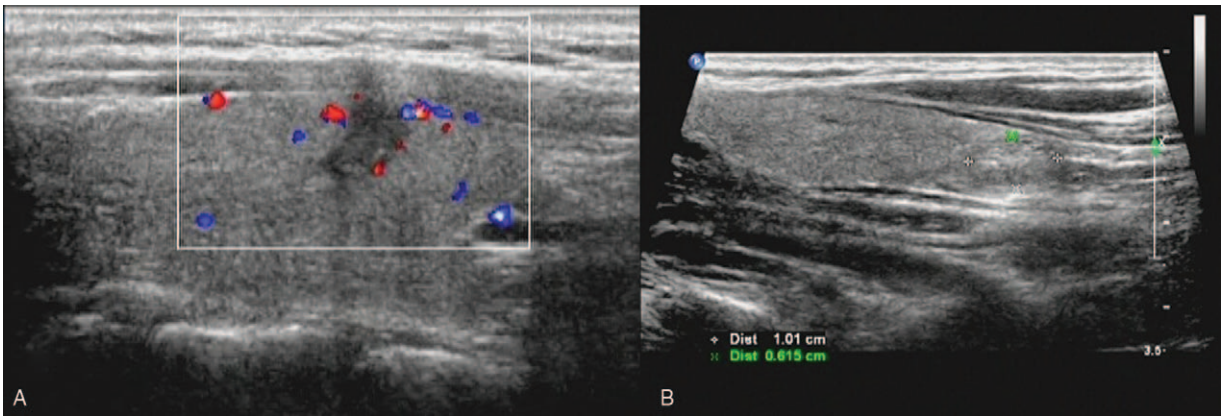

Figure 1. Representative ultrasound image of neck metastasis. (A) Hypoechoic lymph nodes on the right side of the neck. (B) Bilateral cervical lymph node. Short/long axis ratio = 0.609.

or radiotherapy) for carcinoma of head and neck at the West China Hospital, Sichuan University, Chengdu, Sichuan, PR China; the Key Laboratory of Rehabilitation Medicine in Sichuan Province, Chengdu, Sichuan, PR China; the Sichuan Cancer Hospital, Chengdu, China; and the Gong'an County People's Hospital, Gong'an, Hubei, China. Patients with primary stage I and II were subjected to surgery only. Patients of primary stage III were treated by neoadjuvant chemotherapy followed by surgery and chemotherapy (where applicable, 150 mg/ m^2 cisplatin). Patients of primary stage IV were treated by neoadjuvant chemotherapy followed by surgery, chemotherapy, and radiotherapy (where applicable, 62–70 Gy, carboplatin 70 mg/m^2). There were variations in treatment according to the location of the tumor. All 198 patients were available for follow-up in outpatient clinics at the West China Hospital, Sichuan University, Chengdu, Sichuan, PR China; the Sichuan Cancer Hospital, Chengdu, China; and the Gong'an County People's Hospital, Gong'an, Hubei, China during follow-up. The flow diagram of the follow-up period is presented in Figure 2. The demographical and clinical conditions of enrolled patients are reported in Table 1. The most frequent primary tumor site was the larynx, followed by oropharynx, oral cavity, and hypopharynx. At the time of diagnosis, 77 (39%) primary tumors reported stage I, 56 (28%) tumors were primary stage II, 41 (21%) tumors reported primary stage III, and 24 (12%) tumors reported primary stage IV (Table 2).

3.2. Recurrences

During follow-up, a total of 126 (64%) patients were cured after definitive treatment and 72 (36%) patients were reported recurrence. A total of 33 (17%) patients had reported distant metastasis, 24 (12%) patients had reported local recurrence, and 15 (7%) patients had reported regional recurrence. The results of follow-up are reported in Figure 3. The time to detect regional recurrence was shorter than local recurrence (11 ± 1 month vs 25 ± 5 months, $P < .0001$, $q = 15.059$) and distant metastasis (11 ± 1 month vs 18 ± 4 months, $P < .0001$, $q = 7.958$). Also, the time to detect distant metastasis was shorter than local recurrence ($P < .0001$, $q = 9.238$). The details of the times to detect different types of recurrence as per recurrence site are reported in Figure 4.

Hypopharynx carcinoma was reported with highest percentage (15/23; 65%) and the fastest (12 ± 2 months) developed recurrence. Then the following recurrent percentage were oropharynx (32/61; 52%) and oral cavity (18/35; 51%) carcinoma. The least percentage reported recurrent cancer was

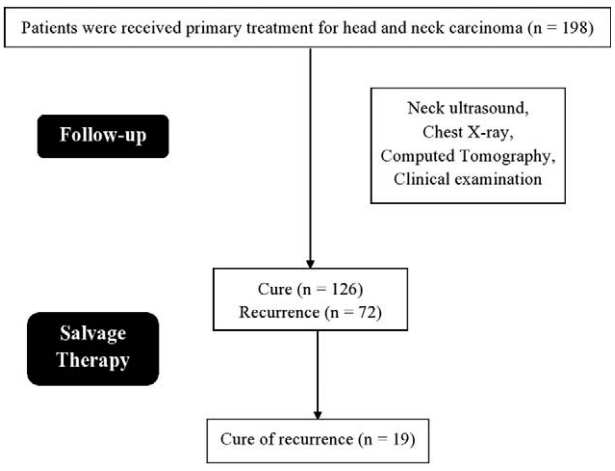

Figure 2. Flow diagram of the follow-up period.

Table 1

Demographical and clinical conditions of patients.

Parameters		Value
Patients included in the analysis		198
Sex	Male	168 (85)
	Female	30 (15)
Age, y	Minimum	21
	Maximum	67
	Mean ± SD	54.15 ± 8.15
Ethnicity	Han Chinese	180 (91)
	Mongolian	15 (7.5)
	Tibetan	2 (1)
	Uighur Muslim	1 (0.5)
Follow-up time, mo	Minimum	6
	Maximum	77
	Mean ± SD	35 ± 1

Categorical data are demonstrated as frequency (percentage) and continuous data are demonstrated as mean ± SD.
SD = Standard Deviation

Table 2

Primary tumor stages and sites.

Primary tumor sites	Primary tumor stage				
	I	II	III	IV	Total
Larynx	31 (16)	22 (11)	17 (8)	9 (4)	79 (39)
Oropharynx	25 (12)	18 (9)	11 (6)	7 (4)	61 (31)
Oral cavity	12 (6)	9 (5)	8 (4)	6 (3)	35 (18)
Hypopharynx	9 (5)	7 (3)	5 (3)	2 (1)	23 (12)
Total	77 (39)	56 (28)	41 (21)	24 (12)	198 (100)

Data are demonstrated as frequency (percentage).

larynx (17/79; 22%). The detailed recurrence as per primary tumor site is reported in Table 3. The time to detect hypopharynx recurrence was shorter than oropharynx recurrence (12 ± 2 months vs 16 ± 4 months, $P < .0001$, $q = 5.479$), oral cavity recurrence (12 ± 2 months vs 17 ± 3 months, $P < .0001$, $q = 6.131$), and larynx recurrence (12 ± 2 months vs 18 ± 3 months, $P < .0001$, $q = 7.259$). There were statistically no significant differences for the time to detect recurrence between oropharynx recurrence and oral cavity recurrence ($P < .0001$, $q = 1.455$), between oropharynx recurrence and larynx recurrence ($P < .0001$, $q = 2.857$), and between oral cavity recurrence and larynx recurrence ($P < .0001$, $q = 1.267$). The details of the times to detect difference types of recurrences according to primary tumor sites are reported in Figure 5.

Primary tumor stage IV (15/24; 63%) had the highest percentage of recurrence followed by stage III (21/41; 51%) and stage II (18/56; 32%). Primary stage I (18/77; 23%) had the lowest percentage of recurrence rate. The details of recurrence as per primary tumor stages are reported in Table 4. A time of detection of recurrence for stage IV tumors was shorter than stage II (12 ± 1 months vs 16 ± 2 months, $P < .0001$, $q = 5.774$) and stage I (12 ± 1 months vs 18 ± 4 months, $P < .0001$, $q = 8.661$). A time of detection of recurrence for stage III tumors was shorter than stage II (14 ± 3 months vs 16 ± 2 months, $P < .0001$, $q = 3.142$) and stage I ($P < .0001$, $q = 6.285$). Also, a time of detection of recurrence for stage II tumors was shorter than stage I (16 ± 2 months vs 18 ± 4 months, $P < 0.0001$, $q = 3.028$). The details of times to detect different types of recurrence as per primary tumor stages are reported in Figure 6.

3.3. Cure of recurrence

A total of 19 (25%) patients had the cure of recurrence. Local recurrence had the highest percentage cure of recurrence (11/24; 46%), followed by regional recurrence. Distant metastasis had the least percentage cure of recurrence (2/33; 6%). The details of the cure of recurrence according to recurrence sites are reported in Table 5.

Stage I primary tumor when reported recurrence, in such conditions, patients had the highest percentage cure of recurrence (9/18; 50%) followed by stage II and stage III. Only 1 (7%) patient of recurrence was cured which had stage IV primary tumor. Tumor of primary stage I and II both had statistically significance cure of recurrence than that of primary stage III and IV. The detailed results of salvage therapy by the primary tumor stage are reported in Table 6.

4. Discussion

Irrespective of definitive treatment used for carcinoma of head and neck, the study was monitored through neck ultrasound during 5-years of a follow-up visit and was reported 36% (72/198) recurrence, which were associated with primary tumor sites and stages. The detailed effect of neck ultrasound in the follow-up care of patients who received definitive treatment for squamous cell carcinoma of head and neck is not reported elsewhere.[2,8] The results of the present study have the same recurrence rate as that of retrospective studies,[1,2] a prospective study,[8] and an observational study[7] but has not the same recurrence rate as that of a cross-sectional study,[4] retrospective studies,[10,11] a prospective study,[12] and case series.[13] The reasons for contradictory results are that the studies on the Turkish population[4] and German population[11] have included the small sample size and less follow-up time, the study on the Korean

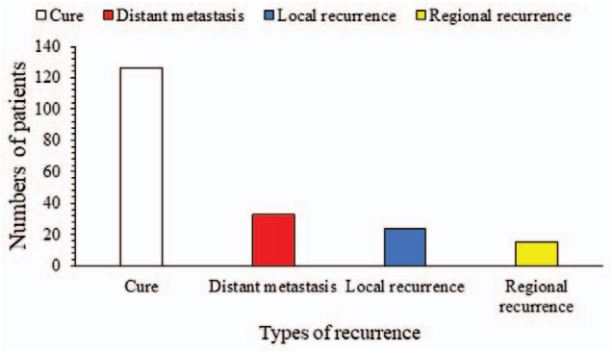

Figure 3. Results of follow-up. Data are presented as frequency.

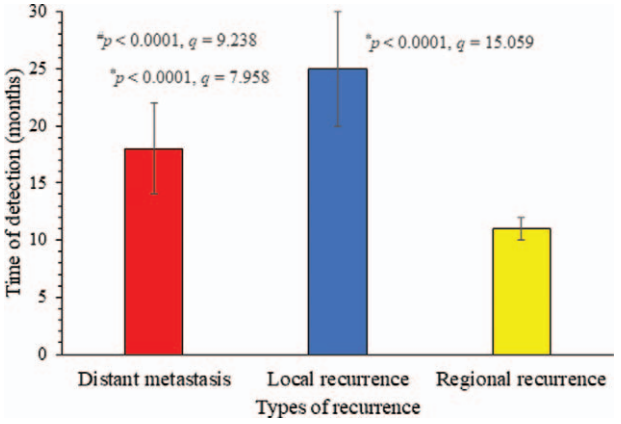

Figure 4. Times to detect different types of recurrence according to recurrence site. Data are presented as mean ± SD. *Significantly higher than regional recurrence. #Significantly lower than local recurrence.

Table 3

Recurrence as per primary tumor site and meantime of detection.

Primary tumor sites			Recurrence			
			Local	Regional	Distant	Total % out of an individual category
Patients reported recurrence			24	15	33	
Hypopharynx			4	2	9	65%
Oropharynx			10	9	13	52%
Oral cavity			4	11	3	51%
Larynx			6	3	8	22%
Comparisons among primary tumor sites	*P*		<.0001	N/A	N/A	N/A
	q -Value	Hypopharynx vs oropharynx	1.575	N/A	N/A	N/A
		Hypopharynx vs oral cavity	1.552	N/A	N/A	N/A
		Hypopharynx vs larynx	5.572	N/A	N/A	N/A
		Oropharynx vs oral cavity	0.1468	N/A	N/A	N/A
		Oropharynx vs larynx	5.484	N/A	N/A	N/A
		Oral cavity vs larynx	4.449	N/A	N/A	N/A

Data are demonstrated as frequency.
N/A = Not applicable.
One-way analysis of variance followed by the Dunnett multiple comparisons test was used for statistical analysis.
A *P* value <.05 and $q > 2.266$ were considered significant.

population[12] is a preoperative diagnostic study, the study on Dutch population[10] has included the large sample size, and case series on the North American population[13] has included follow-up time for 104 days only and not included data of distal metastasis (Table 7). The present study was successful in the detection of recurrence in follow-up period monitoring through neck ultrasound.

The study reported that time to detect regional recurrence was shorter than that of local and distant recurrences. Also, the time to detect hypopharynx recurrence was shorter than that of the other recurrences. The results of the present study were agreed with a retrospective study.[2] The neck ultrasound is successful in the detection of small lymph metastasis and earlier detection of recurrences facilitates rapid salvage therapy.[2] Neck ultrasound is the choice of imaging modality for early detection of regional and hypopharynx recurrences during the follow-up period.

The present study reported a 25% cure of recurrence especially in cases of primary tumor stage I and local recurrences. The results of the present study were agreed with retrospective studies[2,10] but not agreed with a retrospective study.[14] The reasons for such contradictory results are the differences in the inclusion criteria. The study reported a very small amount of success of secondary treatment because of a heterogeneous group of patients with the diseased condition included in the study.[2] The success rate for the cure of recurrence is affected by the primary stage and primary site of carcinoma, not by neck ultrasound diagnosis in the follow-up period.

The quality of life of patients after definitive treatment is not only affected by the diagnosis, treatment, and follow-up care but anxiety and depression are also prevalent in patients during the follow-up period.[2] Fear of recurrence is correlated with psychological morbidity[15] and patients with advanced-stage when dissatisfaction with looks is more depressive.[16] The effects of frequent use of neck ultrasound during follow-up on the psychology of patients are required to evaluate. The other

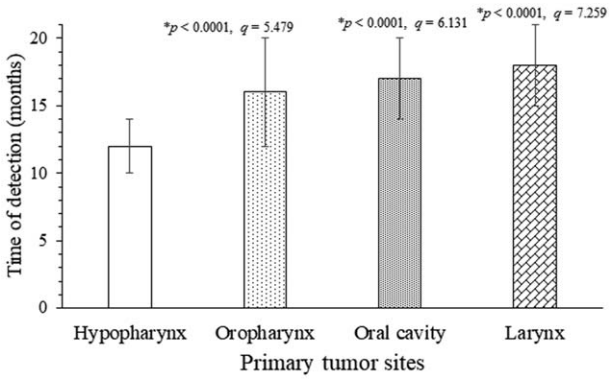

Figure 5. Times to detect different types of recurrence according to primary tumor sites. Data are presented as mean ± SD. *Significantly higher than hypopharynx recurrence.

Table 4

Recurrence as per primary tumor stage.

Primary tumor stage			Patients	Total % out of the individual category
Patients reported recurrence			72	36%
I			18	23%
II			18	32%
III			21	51%
IV			15	63%
Comparisons among different tumor sites	*P*		.006	N/A
	q Value	I vs II	1.159	N/A
		I vs III	4.384	N/A
		I vs IV	5.094	N/A
		II vs III	2.825	N/A
		II vs IV	3.787	N/A
		III vs IV	1.336	N/A

Data are demonstrated as frequency.
N/A = Not applicable.
One-way analysis of variance followed by the Dunnett multiple comparisons test was used for statistical analysis.
A *P* value <05 and $q > 2.266$ were considered significant.

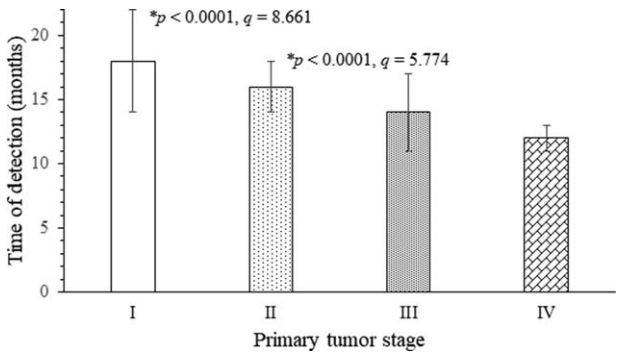

Figure 6. Times to detect different types of recurrence according to the primary tumor stage. Data are presented as mean ± SD. *Significantly higher than primary tumor stage IV.

limitation of the study is that the study is the clinical practice, not a trial. The sensitivity, accuracy, and specificity of ultrasound were not evaluated against computed tomography or magnetic resonance imaging. Mortality and active survival did not report and discuss. The article includes all head and neck primary site tumors and not includes the thyroid tumors and lymphoma; the applicability of the article becomes limited.

5. Conclusions

The monitoring through neck ultrasound is reported to be effective for detection of recurrence in 5 years of the follow-up period of patients who received primary treatment for carcinoma of head and neck especially regional recurrence and primary tumor stage I. The success rate for the cure of recurrence is affected by the primary stage and site of carcinoma. Maxillofacial and Ear Nose Throat surgeons can use the finding from the present study for the diagnosis of recurrence in the follow-up period to avoid under- or overtreatment in patients who received definitive treatment for carcinoma of head and neck. The retrospective study is applicable in terms that ultrasound is the most accessible method among the computed tomography and magnetic resonance imaging for detection of head and neck carcinoma in follow-up care for patients. There is also logic in demonstrating the use of ultrasound in the follow-up of lymph nodes metastasis.

Table 5

Results of salvage therapy by recurrence sites.

Recurrence site			Patients	Cure of recurrence	Total % cure of recurrence out of an individual category
Patients reported recurrence			72	19	25%
Distant metastasis			33	2	6%
Local recurrence			24	11	46%
Regional recurrence			15	6	40%
Comparisons among recurrence site	*P*		.001	N/A	N/A
	q Value	Distant metastasis vs local recurrence	5.149	N/A	N/A
		Distant metastasis vs regional recurrence	3.786	N/A	N/A
		Local recurrence vs regional recurrence	0.617	N/A	N/A

Data are demonstrated as frequency.
N/A = not applicable.
One-way analysis of variance followed by the Dunnett multiple comparisons test was used for statistical analysis.
A *P* value <.05 and $q > 2.266$ were considered significant.

Table 6

Results of salvage therapy as per primary tumor stage.

Primary tumor stage			Patients	Cure of recurrence	Total % cure of recurrence out of an individual category
Patients reported recurrence			72	19	25%
I			18	9	50%
II			18	7	39%
III			21	2	10%
IV			15	1	7%
Comparisons among primary tumor stage	*P*		.004	N/A	N/A
	q Value	I vs II	1.145	N/A	N/A
		I vs III	4.329	N/A	N/A
		I vs IV	4.259	N/A	N/A
		II vs III	3.141	N/A	N/A
		II vs IV	3.167	N/A	N/A
		III vs IV	0.291	N/A	N/A

Data are demonstrated as frequency.
N/A = not applicable.
One-way analysis of variance followed by the Dunnett multiple comparisons test was used for statistical analysis.
A *P* value <.05 and $q > 2.266$ were considered significant.

Table 7

Overview of data for studies of the head and neck carcinomas.

Population and reference no.	Modality	Study design	Monitoring follow-up time	Study population included	Reported recurrence
Japanese population[1]	Neck ultrasound	A retrospective study	5 y	72 Patients	44%
German population[2]	Neck ultrasound	A retrospective study	3 –y	140 Patients	35%
Turkish population[4]	Ultrasound elastography and contrast-enhanced computed tomography	A cross-sectional study	Pre-surgery study	23 Patients	57%
Spanish population[7]	Neck ultrasound	An observational study	7 y	90 Patients	39%
Taiwanese population[8]	Three-dimensional ultrasound, magnetic resonance imaging, ^{18}F-fluorodeoxyglucose positron emission tomography, computed tomography	A prospective study	Preoperative study	52 Patients	40%
Dutch population[10]	Ultrasound-guided fine-needle aspiration cytology	A retrospective study	87 wk	540 Patients	23%
German population[11]	Three-dimensional ultrasound, magnetic resonance imaging, ^{18}F-fluorodeoxyglucose positron emission tomography, and computed tomography	A prospective study	3 mo	25 Patients	54%
Korean population[12]	Three-dimensional ultrasound, magnetic resonance imaging, ^{18}F-fluorodeoxyglucose positron emission tomography, and computed tomography	A prospective study	Preoperative study	67 Patients	18%
North American population[13]	Three-dimensional ultrasound, magnetic resonance imaging, ^{18}F-fluorodeoxyglucose positron emission tomography, and computed tomography	A prospective study	104 days	73 Patients	20%

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Writing – original draft: Jifeng Liu.
Writing – review & editing: Jifeng Liu.

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