

Tumor regression patterns by follow-up duration in patients with nasopharyngeal carcinoma treated with concurrent chemoradiotherapy

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ABSTRACT

The aim of this study was to describe the patterns of tumor regression with respect to follow-up duration after chemoradiotherapy in patients with nasopharyngeal carcinoma. A total of 27 patients with nasopharyngeal carcinoma were included and received definitive concurrent chemoradiotherapy. Patterns of primary tumor regression and development of locoregional recurrences were evaluated by imaging studies every 1 to 2 months. Primary tumors gradually regressed over the period of follow-up. The median time to full regression was 4.9 months (range, 1.5–19.4). In 61.5% of patients, the primary tumor continued to regress for >4 months after completion of chemoradiotherapy. Six patients experienced locoregional recurrence during follow-up, all of which occurred after full regression of the primary tumor. A patient group with delayed regression did not have poorer prognosis than a patient group with early regression. Older age, non-current-smoker status, advanced T stage, and higher daily radiation dose were significantly associated with delayed primary tumor regression. Nasopharyngeal carcinoma continued to regress for >4 months after chemoradiotherapy in a considerable number of patients. We recommend waiting for >4 months for full regression of nasopharyngeal carcinomas after chemoradiotherapy, if signs of persistent or recurrent disease are not evident on follow-up examination.

KEYWORDS: nasopharyngeal carcinoma, radiotherapy, regression

INTRODUCTION

Radiotherapy (RT) with or without chemotherapy is the mainstay treatment for patients with nasopharyngeal carcinoma. Accurate evaluation of RT response is important for increasing the efficacy of salvage treatment for persistent or recurrent disease. To accurately evaluate the response to RT in patients with nasopharyngeal carcinoma, deciding appropriate evaluation timing is important. Too early evaluation of the response to RT could result in overtreating some patients whose disease is regressing slowly, whereas too late evaluation of the response could decrease the efficacy of the salvage treatment for potentially persistent disease. Some studies have proposed cut-off times for evaluating RT response in patients with nasopharyngeal carcinoma [1, 2]; however, no definite consensus exists on the proper time for evaluation.

Determining the appropriate timing of RT response evaluation requires an understanding of the patterns of tumor regression with

respect to follow-up duration after RT in patients with nasopharyngeal carcinoma. Until now, no study has addressed patterns of tumor regression in nasopharyngeal carcinoma after RT or chemo-RT. In this study, we have described the patterns of tumor regression with respect to follow-up duration after chemo-RT in patients with nasopharyngeal carcinoma.

MATERIALS AND METHODS

Inclusion criteria were histologically proven nasopharyngeal carcinoma, receipt of definitive concurrent chemo-RT with or without induction chemotherapy, Eastern Cooperative Oncology Group performance status ≤ 2 , no previous history of head-and-neck area irradiation, no distant metastasis, follow-up ≥ 12 months, and available follow-up data. Patients who received adjuvant chemotherapy

and patients who received palliative RT were excluded. From January 2007 to March 2015, 51 patients with nasopharyngeal carcinoma received RT or chemo-RT at our institution. Of these patients, 27 met the required criteria and were included.

Pretreatment evaluation consisted of complete history and physical examination, nasopharyngeal fiberoscopy, complete blood and biochemistry counts, liver and renal function tests, dental evaluations, computed tomography (CT) scans and magnetic resonance imaging (MRI) of the head-and-neck region, and positron emission tomography (PET). Bone scans and CT scans of the chest and/or abdomen were performed only when clinically indicated. For each patient, cancer stage was restaged according to the 7th edition of the American Joint Committee on Cancer staging system. Histology was classified according to the World Health Organization system. We retrospectively reviewed hospital records, laboratory records, and imaging studies. The Institutional Review Board of our institution approved this study, and all research was carried out in compliance with the Declaration of Helsinki.

All patients received CT-planned RT with either 3D conformal RT (3D-CRT) or intensity-modulated RT (IMRT). The choice between 3D-CRT and IMRT was determined by the physician based on tumor spread, and the patient's preference and general condition. The gross tumor volume (GTV) included the gross extent of the primary tumor and grossly involved cervical lymph nodes visualized on CT, MRI and/or PET. The high-risk clinical target volume (CTV) was defined as the GTV plus a 1–1.5 cm margin to account for subclinical tumor spread. The CTV usually encompassed the entire nasopharyngeal mucosa together with areas suspected of being at risk in the skull base, parapharyngeal spaces, inferior sphenoid sinuses, posterior nasal cavity and posterior maxillary sinuses. The low-risk CTV was defined as the total volume of prophylactically treated neck lymph nodes. The planning target volume (PTV) was created by adding an additional 5 mm margin to the CTV. The prescription dose was determined by the physician, based on tumor stage, the patient's general condition and the probability of RT-induced toxicity. The high-risk PTV was treated with a daily dose of 1.8–2.2 Gy and a total dose of 63–73.5 Gy. The low-risk PTV was treated with a daily dose of 1.65–2 Gy and a total dose of 45–54 Gy. For standard comparison of various RT dose schedules, biologically equivalent doses were calculated using a linear quadratic model with α/β ratio 10. The 3D-CRT used a Clinac iX (Varian Medical System Inc., Palo Alto, CA, USA) and IMRT used a TomoTherapy (Accuray Inc., Madison, WI, USA) with the simultaneous integrated boost technique. Treatment plans were evaluated from dose–volume histograms and by visually inspecting isodose curves. In general, we considered plans to be acceptable if the PTV was covered by 95% isodose curves, inhomogeneity for the PTV ranged from 95 to 107%, and doses to critical normal organs were limited in their tolerances.

All patients received concurrent chemotherapy during the course of the RT as a regimen of intravenous administration of cisplatin (100 mg/m²) every 3 weeks, starting on the day of RT initiation. The decision to use neoadjuvant chemotherapy before concurrent chemo-RT was made by a multidisciplinary team after discussion between radiation, surgical and medical oncologists. The

neoadjuvant chemotherapy regimen was a docetaxel/cisplatin/5-fluorouracil combination.

Primary tumor regression patterns were evaluated by CT and/or MRI with intravenous contrast agent every 1 to 2 months. All images were interpreted by two radiologists with >10 years of experience reviewing CT and MRI of the head and neck regions. Discrepancies in interpretation were resolved by a multidisciplinary team after discussion between the two radiologists. Full regression was defined as the stage at which the enhanced primary tumor lesion did not decrease any more, or disappearance of the enhanced primary tumor lesion. Total regression was defined as disappearance of the enhanced primary tumor lesion. All patients were evaluated until their primary tumor reached full or total regression. The times to full regression and total regression were calculated from the date of RT completion to the date of the imaging study used for final regression status determination.

In-field locoregional recurrence was defined as increased size of arterial enhancing lesions or appearance of new lesions within the PTV. Out-field locoregional recurrence was defined as appearance of new lesions outside the PTV in the head-and-neck region. Distant metastasis was defined as evidence of tumor in any other area. The patients who experienced locoregional recurrence or distant metastasis received salvage treatment, such as RT, surgery, or chemotherapy if it was possible.

Actuarial rates were estimated using the Kaplan–Meier method, and groups were compared by log-rank test for univariate analysis. Factors that influenced time to full regression were analyzed. Parameters with a *P*-value of less than 0.50 in a univariate analysis were further assessed in a multivariate analysis, using a Cox proportional hazard model. For all analyses, a *P*-value < 0.05 was considered statistically significant. All analyses were performed using PASW ver. 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient and tumor characteristics are summarized in Table 1. The most commonly prescribed dose fractionation schedule was a total dose of 70 Gy, with daily dose of 2 Gy; eight patients (29.6%) were treated with this fractionation schedule. Six patients (22.2%) experienced temporary RT interruption because of treatment toxicity. In two patients (7.4%), RT was interrupted for 3 days because of Grade 3 mucositis. RT was interrupted in three patients (11.1%) for 14 days because of Grade 3 hematologic toxicity. One patient experienced RT interruption for 23 days because of Grade 3 mucositis, general weakness, and poor oral intake. The median follow-up period was 59.7 months (range, 12.3–110.0). During the follow-up period, 24 patients remained alive, and the 2- and 5-year overall survival rates were 96.0% and 87.5%, respectively. Four patients experienced distant metastases. The metastatic sites were lung in three patients, and bone and brain in one patient. The 2- and 5-year distant metastasis-free survival rates were both 84.7%.

Primary tumor regression status after chemo-RT is summarized in Fig. 1. In one patient, the total diameter of the viable primary tumor increased on the first follow-up imaging study. The other 26 patients showed primary tumor regression after chemo-RT. The

Table 1. Patient and tumor characteristics (n = 27)

Characteristics	Value (%)
Age (years)	Median 49.5 (range, 34.5–70.5)
Gender	
Male/female	21 (77.8)/6 (22.2)
ECOG performance status	
0/1/2	5 (18.5)/18 (66.7)/4 (14.8)
Smoking status	
Current/previous/never	16 (59.3)/3 (11.1)/8 (29.6)
Alcohol status	
Current/previous/never	19 (70.4)/2 (7.4)/6 (22.2)
WHO histology ^a	
I/II/III	11 (40.7)/4 (14.9)/12 (44.4)
T stage	
1/2/3/4	3 (11.2)/11 (40.7)/6 (22.2)/7 (25.9)
AJCC stage	
2/3/4A/4B	4 (14.9)/15 (55.6)/6 (22.2)/2(7.3)
RT technique	
IMRT/3D-CRT	13 (48.1)/14 (51.9)
Total RT dose (BED, Gy ₁₀)	Median 82.6 (range, 74.3–88.9)
RT duration (weeks)	Median 7.4 (range, 6.2–10.2)
Induction chemotherapy	
Yes/no	13 (48.1)/14 (51.9)

ECOG = Eastern Cooperative Oncology Group, WHO = World Health Organization, AJCC = American Joint Committee on Cancer Staging, RT = radiotherapy, IMRT = intensity-modulated radiotherapy, 3D-CRT = 3D conformal radiotherapy, BED = biologically equivalent dose.

^aWHO histology I = keratinizing squamous cell carcinoma, WHO histology II = non-keratinizing carcinoma, differentiated type, WHO histology III = non-keratinizing carcinoma, undifferentiated type.

median time to full regression was 4.9 months (range, 1.5–19.4). Except for 4 patients whose primary tumors fully regressed within 2 months, the primary tumors continued to regress for >2 months after treatment in 22 patients (84.6%). Of the 26 patients who showed primary tumor regression, 21 eventually experienced total primary tumor regression during the follow-up period. The median time to total regression of the primary tumor was 4.1 months (range, 1.5–15.2). Of the 21 patients with total primary tumor regression, 16 (80.9%) showed total regression after 2 months of chemo-RT completion (Fig. 2). Of the 26 patients who showed primary tumor regression, 5 did not reach total regression. The follow-up periods and clinical outcomes at last follow-up of these 5 patients are summarized in Table 2.

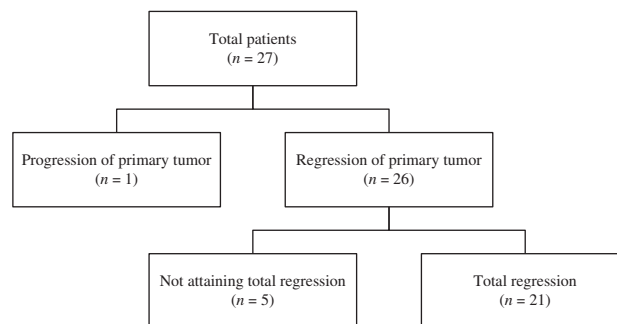


Fig. 1. Schematic summary of primary tumor regression after chemoradiotherapy in patients with nasopharyngeal carcinoma. Of the 27 patients in the study, 26 showed regression of the primary tumor, and 21 showed total regression.

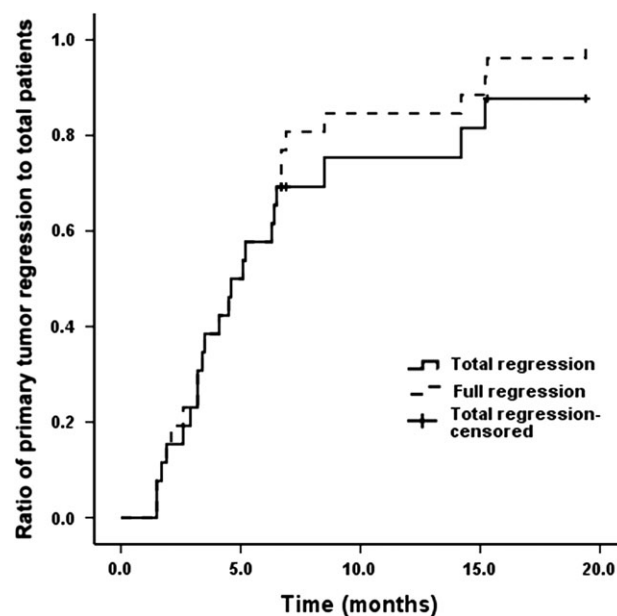


Fig. 2. Development patterns of full and total primary tumor regression with reference to follow-up duration after concurrent chemoradiotherapy in patients with nasopharyngeal carcinoma. Of the 26 patients who showed regression of the primary tumor, 5 did not reach total regression. The median times to full and total regression were 4.9 months (range, 1.5–19.4) and 4.1 months (range, 1.5–15.2), respectively.

Six patients experienced locoregional recurrence. The locoregional recurrence-free survival rates were 80.8% for 2 years and 76.8% for 5 years. Development patterns for locoregional recurrences are summarized in Table 3. Except for one patient who experienced primary tumor progression on the first follow-up imaging, all patients had in-field and/or out-field locoregional recurrences after full primary tumor regression.

Table 2. Clinical outcomes for five patients who did not reach total primary regression

Sex/age	Time to full regression (months)	Follow-up period (months)	Clinical outcome at last follow-up
M/58.6	6.9	18.2	Locoregional recurrence
M/47.2	6.7	31.2	Locoregional recurrence
M/38.2	15.3	94.1	No evidence of disease
M/34.5	19.4	108	No evidence of disease
M/46.7	6.7	24.8	Locoregional recurrence, distant metastasis

Table 3. Development patterns of locoregional recurrence (n = 6)

Sex/age	Time to full regression (months)	Time to recurrence (months)	
		In-field locoregional recurrence	Out-field locoregional recurrence
F/49.5	Progression of primary tumor	1.5	1.5
M/58.6	6.9	9.2	9.2
M/47.2	6.7		13.2
M/46.7	6.7		8.1
F/40.1	6.4	27.3	27.3
M/46.3	1.5	22.1	

F = female; M = male.

The survival rates according to speed of primary tumor regression were analyzed for the 26 patients with primary tumor regression (Table 4). Compared with a patient group with early primary tumor regression (time to full regression ≤ 5 months), the patient group with delayed regression (time to full regression > 5 months) had lower rates of overall survival, locoregional recurrence-free survival and distant metastasis-free survival. However, the differences between the groups were not significant. We also analyzed factors that influenced the length of time to full regression (Table 5). In univariate analysis, age, smoking status, and T stage were significantly associated with length of time to full regression. In multivariate analysis, smoking status (hazard ratio, 0.206; 95% confidence interval, 0.102 to 0.725; $P = 0.018$) and T stage (hazard ratio, 0.086; 95% confidence interval, 0.036 to 0.349; $P = 0.020$) remained significant factors. In addition, daily RT dose was significantly associated with length of time to full regression in multivariate analysis (hazard ratio, 0.139; 95% confidence

Table 4. Survival analyses according to the speed of primary tumor regression (n = 26)

Survival	Time to full regression		P-value
	≤ 5 months	> 5 months	
Overall survival (%)			
2-year	100	100	0.120
5-year	100	80.8	
Locoregional recurrence-free survival (%)			
2-year	91.7	76.2	0.130
5-year	91.7	67.7	
Distant metastasis-free survival (%)			
2-year	91.7	84.6	0.493
5-year	91.7	84.6	

interval, 0.039 to 0.786; $P = 0.041$). Older age, non-current smoker status, advanced T stage, and higher daily RT dose were associated with delayed primary tumor regression in patients with nasopharyngeal carcinoma.

DISCUSSION

A previous study reported tumor regression patterns according to follow-up duration after RT in patients with nasopharyngeal carcinoma, using repeated nasopharyngeal biopsies [2]. In that study, 803 patients with nasopharyngeal carcinoma underwent serial biopsies after definitive RT. Those patients with positive histology underwent repeated biopsies every 2 weeks for 3 months after completion of RT until biopsy results were negative. In that study, 617 (76.8%) patients showed negative histology in the first biopsy session. The other 186 (23.2%) showed continuous spontaneous histological remission on repeat biopsies after initial positive histology during follow-up. With increasing follow-up time after RT, the histologic remission incidence increased, and 131 patients subsequently attained negative histology; 55 patients had persistent disease at 3 months after RT completion, and salvage treatment was initiated for these patients. However, post-RT multiple biopsies of heavily irradiated tissue may cause trauma and superimposed infection, and may exacerbate post-RT toxicities [3]. Therefore, for analyzing tumor regression patterns after RT in patients with nasopharyngeal carcinoma, additional study is needed using methods that are alternative or complementary to multiple biopsies. Imaging is important for post-treatment evaluation of patients with head-and-neck cancer. Among the various imaging modalities, CT and MRI are the most popular because of their rapid image acquisition and superior contrast resolution [4, 5]. Our study used CT and MRI to describe tumor regression patterns with respect to follow-up duration after chemo-RT in patients with nasopharyngeal carcinoma. In our results, primary tumor regression patterns evaluated with CT and/

Table 5. Analysis of predictive factors for length of time to full primary tumor regression

Variables	Median time to full regression (months)	P-value	
		Univariate	Multivariate
Age (years)			
<50 vs ≥50	4.1 vs 6.4	0.040	0.062
Sex			
Male vs female	4.5 vs 5.9	0.849	
Smoking status			
Current vs previous or never	3.4 vs 6.4	0.028	0.018
WHO histology			
1 vs 2–3	3.4 vs 5.1	0.873	
T stage			
1–2 vs 3–4	3.2 vs 6.7	0.004	0.020
RT technique			
IMRT vs 3D-CRT	5.1 vs 4.1	0.849	
Daily RT dose (Gy)			
≤1.8 vs >1.8	4.1 vs 4.6	0.417	0.041
Total RT dose (BED, Gy ₁₀)			
≤82 vs >82	5.1 vs 4.5	0.422	0.245
RT duration (weeks)			
≤7 vs >7	4.6 vs 4.5	0.204	0.592
RT interruption			
Yes vs no	4.6 vs 5.2	0.629	
Induction chemotherapy			
Yes vs no	4.6 vs 4.1	0.973	

WHO = World Health Organization, RT = radiotherapy, IMRT = intensity-modulated radiotherapy, 3D-CRT = 3D conformal radiotherapy, BED = biologically equivalent dose.

or MRI seemed to be slower than patterns evaluated with repeated biopsies. In our study, the median time to full regression was 4.9 months, and only 8 patients (30.8%) showed full primary tumor regression within 3 months of chemo-RT completion. The other 18 patients showed full regression after 3 months of chemo-RT completion (Fig. 2). In Kwong *et al.*'s study [2], 93.2% of patients showed complete histological remission within 3 months after RT. The histologic processes of radiation begin immediately after radiation exposure, although the clinical features evaluated by imaging

studies may not become apparent for weeks or months after radiation exposure [6]. The other possible reason for different regression patterns between our study and that of Kwong *et al.* is the frequency of evaluation for treatment response. In a study by Kwong *et al.*, the histologic remission status was evaluated every 2 weeks. Because we evaluated primary tumor regression patterns every 1 to 2 months, we might have detected full primary tumor regression later than their actual occurrence. In addition, all patients in our study received concurrent chemo-RT, whereas patients in Kwong *et al.*'s study received RT alone. In our previous study, head-and-neck cancer patients treated with concurrent chemo-RT showed delayed primary tumor regression compared with patients treated with RT alone, although these differences were not statistically significant and the exact mechanism remains unclear [7].

Several studies have reported treatment outcomes for patients with nasopharyngeal carcinoma after RT or chemo-RT. However, the cut-off times for treatment response evaluation vary substantially among those studies, ranging from 1 to 4 months [4, 5, 8–13]. Our study described primary tumor regression patterns according to follow-up duration and calculated time from chemo-RT completion to full primary tumor regression in patients with nasopharyngeal carcinoma. According to our results, although time to full regression varied between individuals, primary tumors continuously regressed for >4 months after chemo-RT completion in 61.5% of the patient population (Fig. 2). Except for one patient who experienced primary tumor progression on the first follow-up image, all locoregional recurrences developed after full primary tumor regression (Table 3). In addition, survival outcomes for patients with delayed regression were not significantly different from those of patients with early regression (Table 4). Although the exact radiobiological mechanism by which tumor regression speed influences prognosis remains unknown, several previous studies have also reported that delayed tumor regression is not a factor associated with poor prognosis in nasopharyngeal carcinoma [2, 8]. Primary tumors must be allowed to fully regress after RT for exact evaluation of treatment response. Because a substantial number of patients showed continuous regression of primary tumors without additional treatment for >4 months after chemo-RT, and all locoregional recurrences developed after full tumor regression, we recommend that frequent biopsies should be carefully implemented early in the course of follow-up. We also recommend waiting for full primary tumor regression for >4 months after chemo-RT completion if signs of persistent or recurrent disease are not evident on clinical and/or imaging follow-up examinations.

In our analysis, age, smoking status, T stage, and daily RT dose were significant predictive factors for length of time to full primary tumor regression. Older age (≥50 years), non-current smoker status, advanced T stage (T3–4), and higher daily RT dose were significantly associated with delayed primary tumor regression. We also analyzed predictive factors for delayed primary tumor regression in our previous studies on patients with head-and-neck squamous cell carcinoma and hepatocellular carcinoma [7, 14]. Older age and higher daily RT dose were also associated with delayed regression in those studies. Advanced T stage was associated with delayed regression in our previous study on patients with head-and-neck squamous cell carcinoma [7]. In our previous study of hepatocellular carcinoma, T stage was not analyzed as a potential

predictive factor for delayed regression of primary tumor [14]. However, the results for smoking status are contradictory in our current and previous studies. In this study, non-current-smoker status was significantly associated with delayed primary tumor regression in univariate- and multivariate analyses, whereas in our previous study, current smoker status was associated with delayed primary tumor regression in patients with head-and-neck squamous cell carcinoma (but without statistical significance). At the present time, we are unable to draw conclusions about the predictive factors for tumor regression speed because of so few existing relevant studies. To confirm our results, further studies are warranted.

This study had some limitations. First, the retrospective design may have inherent biases. For instance, tumor regression was evaluated at the physician's discretion rather than with timing based on established protocol. Therefore, the time of imaging study acquisition varied among patients. However, we frequently conducted imaging studies on all patients to effectively evaluate regression patterns. Second, the sample size was small, so we may not have detected minor differences in our statistical analysis. Third, because RT fractionation schedules and the implementation of neoadjuvant chemotherapy were decided by physicians rather than by established protocols, patient and tumor characteristics were heterogeneous. However, we believe our results address some unresolved issues regarding the management of nasopharyngeal carcinoma.

In conclusion, nasopharyngeal carcinoma continued to regress for >4 months after chemo-RT in a considerable number of patients, and all locoregional recurrences developed after full primary tumor regression. We recommend waiting for >4 months after completion of chemo-RT for full regression of nasopharyngeal carcinoma if signs of persistent or recurrent disease are not evident on follow-up examinations.

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None.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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