Lung Metastasis Alone in Nasopharyngeal Carcinoma: A Relatively Favorable Prognostic Group

A Study by the Hong Kong Nasopharyngeal Carcinoma Study Group

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BACKGROUND. The current study was conducted to examine the pattern and the predictive factors of distant metastases (DM) in patients with nasopharyngeal carcinoma (NPC) after primary radiotherapy treatment.

METHODS. Data from all five regional cancer centers in Hong Kong were collected retrospectively and pooled for the current study, which was coordinated by the Hong Kong Nasopharyngeal Carcinoma Study Group. The sample was comprised of all 2915 patients with NPC without DM at the time of presentation who were treated with radiotherapy in 1 of the 5 cancer centers during the period between January 1996 and December 2000.

RESULTS. DM was found to be the leading cause of NPC failure, with a 5-year actuarial rate of 14.9% in this patient cohort. Despite the poor overall survival (OS) of these patients, those with lung metastasis alone represented a distinctive group associated with a significantly better OS. International Union Against Cancer (UICC) N classification, UICC T classification, advanced age, and male gender were found to be significant and independent determinants for DM.

CONCLUSIONS. Long-term survival is possible in patients with distant metastatic NPC confined to the lung. An aggressive approach to treatment for this group of patients should be considered. ***Cancer* 2004;101:300–6.**

KEYWORDS: nasopharyngeal carcinoma (NPC), distant metastases (DM), lung metastasis, prognosis.

Distant metastases (DM) have been recognized to be a major cause of treatment failure in patients with nasopharyngeal carcinoma (NPC). With the prospect of improvement in local control with the increasing application of high-precision radiotherapy, distant failure is expected to become an increasingly predominant cause of death from NPC.[1,2] Metastatic NPC appears to be a heterogeneous group of tumors with a wide range of survival. Previous reports have described a small number of patients with metastatic NPC who achieved long-term disease-free survival after aggressive multimodality therapy.[3–6] To better understand this heterogeneity in patients treated in the contemporary era, we set out to investigate the survival of patient groups with respect to involved organs and in relation to the occurrence or otherwise of locoregional failure. We also attempted to define the predictive factors of DM so as to facilitate the selection of the appropriate high-risk group to receive combined modality therapy as their primary treatment.

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MATERIALS AND METHODS

Patients

The Hong Kong Nasopharyngeal Carcinoma Study Group (HKNPCSG) is comprised of representatives from all five oncology centers under the Hospital Authority in Hong Kong: Queen Elizabeth Hospital (QEH), Prince of Wales Hospital (PWH), Tuen Mun Hospital (TMH), Queen Mary Hospital (QMH), and Pamela Youde Nethersole Eastern Hospital (PYNEH). Data regarding patients treated at the five centers were collected retrospectively and pooled for the current study. During the period between January 1996 and December 2000, there was a total of 2915 patients with a confirmed histologic diagnosis of NPC who were without evidence of DM at the time of presentation (Stage M0) and who were treated with curative-intent radiotherapy in 1 of the 5 oncology centers: 628 patients at QEH, 690 patients at PWH, 618 patients at TMH, 519 patients at QMH, and 460 patients at PYNEH. These patients comprised the sample of the current retrospective study.

The histology in 98.5% of the patients was nonkeratinizing or undifferentiated carcinoma (World Health Organization [WHO] type 2 or 3 histology[7]). Patient characteristics are shown in Table 1. The median duration of follow-up for the entire cohort was 3.1 years (range, $<$ 0.1 to 6.6 years).

TABLE 1
Characteristics of 2915 Patients with NPC

Characteristics	No. of patients (%)
Age (yrs)	
$<$ 40	694 (23.8)
$\geq$ 40	2221 (76.2)
Gender	
Male	2099 (72.0)
Female	816 (28.0)
Histology	
WHO type 1 (keratinizing carcinoma)	10 (0.3)
WHO type 2 (nonkeratinizing carcinoma)	280 (9.6)
WHO type 3 (undifferentiated carcinoma)	2593 (88.9)
UICC T classification	
T1	467 (16.0)
T2	1476 (50.6)
T3	469 (16.1)
T4	503 (17.3)
UICC N classification	
N0	804 (27.6)
N1	1223 (42.0)
N2	517 (17.7)
N3	371 (12.7)
UICC overall stage grouping	
I	199 (6.8)
II	1174 (40.3)
III	741 (25.4)
IV	801 (27.5)
Chemotherapy	
Neoadjuvant	244 (8.4)
Concurrent	420 (14.4)
Adjuvant	237 (8.1)
Any chemotherapy	681 (23.4)
Boost	
Parapharyngeal boost	1493 (51.2)
Intracavitary brachytherapy	320 (11.0)
Any boost	1786 (61.3)

NPC: nasopharyngeal carcinoma; WHO: World Health Organization; UICC: International Union Against Cancer.

Clinical Staging and Oncologic Treatment

All patients were staged by clinical examination, computed tomography scan of the nasopharynx and upper neck, nasopharyngoscopy, chest radiography, and serum alkaline phosphatase level. In addition, magnetic resonance imaging of the nasopharynx and neck was performed in 33% of patients. Stage was defined according to the American Joint Committee on Cancer [AJCC]/International Union Against Cancer [UICC] 1997 stage classification for NPC.[8] Details regarding lymph node involvement were recorded routinely in purpose-specific diagrams, allowing for the retrospective determination of lymph node stage according to the 1997 stage classification if this was not applied initially. Imaging screening for DM was not mandatory and was performed only in those patients with suspicious clinical symptoms or abnormal baseline investigations. In two centers (QMH and PWH), routine imaging screening for DM was performed for patients with N3b disease.

All 5 centers used the Ho technique as the primary radiotherapy for the majority of patients (88.7%) during the study period. The radiotherapy techniques have been described in previous publications.[9] The median dose to the primary tumor was 66 grays (Gy). A "parapharyngeal boost" of 10–20 Gy was given to patients with parapharyngeal extension of disease[10] and an intranasopharyngeal brachytherapy boost was given selectively to patients with T1 or T2a disease (either for residual disease or on an adjuvant basis),[11] and a conformal radiotherapy boost was given to some patients with advanced T-classified disease. Neoadjuvant/concurrent/adjuvant chemotherapy, which was nearly exclusively cisplatin-based, was given to 681 patients with advanced stage disease (23%) (Table 1).

Outcome Assessment and Statistical Methods

The clinical endpoints included local failure (LF; recurrences at the nasopharynx), regional failure (RF; recurrences at regional neck lymph nodes), DM, and death. Patients who developed DM were categorized

further into three groups: 1) "DM-only" (those patients who had DM without LF or RF); 2) "LF/RF → DM" (those patients with LF or RF preceding the diagnosis of distant metastasis by > 2 months [the 2-month period was the usual time required to complete the full staging investigations for confirming the extent of DM]); and 3) "LF/RF + DM" (those patients with DM concurrent with or followed by LF or RF).

All time-to-event endpoints were calculated from the first day of primary radiotherapy to the date of occurrence of that event, or censored at the date of last follow-up. The median time intervals from primary radiotherapy to first DM reported in different subgroups were compared using the Student *t* test. The overall survivals of different subgroups were plotted by the Kaplan–Meier method and compared with the log-rank test. The predictive factors for DM were analyzed by the time to first DM with the Kaplan–Meier method and the log-rank test. The Cox proportional hazards model was used for the multivariate analysis. The clinical parameters used in the analysis included patient's age, gender, histology type, UICC T classification, and UICC N classification. Age was analyzed as a continuous variable. The use of chemotherapy was not analyzed in the current study because it was selected for patients with advanced disease and the selection criteria were not exactly uniform among centers. The statistical analysis was performed with SAS software (version 8.02; SAS Institute Inc., Cary, NC). All significance tests were two-sided with P values < 0.05 considered to be significant.

RESULTS

Treatment Outcome

Of the 2915 patients treated with curative-intent radiotherapy with or without chemotherapy, 1705 patients (58%) were alive without evidence of disease at the time of last follow-up, 608 patients (21%) were alive with disease, and 45 patients (2%) were alive with unknown disease status. A total of 408 patients (14%) had died of NPC, 21 of whom had died of treatment-related complications.Seventy-five patients had died of intercurrent illness. In 74 patients, the cause of death could not be determined. A total of 338 patients (12%) had developed LF, 100 patients (3%) had developed RF, and 476 patients (16%) had developed DM. Combined locoregional and distant failures occurred in 3% of patients. DM was found to be the most common mode of failure, with a 5-year actuarial rate of 14.9% reported in the current study cohort.

TABLE 2
Time Course of NPC Failures

Modes of failure	No. of patients	Median time interval from primary RT to first failure (yrs) (25–75 percentile)	Median OS from primary RT (yrs) (95% CI)
DM only	379	1.1 (0.63–1.96)	2.1 (1.96–2.45)
Bone only	84	0.8 (0.40–1.30)	1.7 (1.30–2.54)
Liver only	61	1.0 (0.65–1.82)	1.9 (1.53–2.19)
Lung only	41	1.6 (1.03–2.35)	3.9 (3.10–a)
More than one organ	139	1.1 (0.61–2.02)	2.3 (1.99–2.91)
Others/unclassified	54	1.2 (0.78–1.94)	1.87 (1.53–2.45)
DM with LF/RF			
LF/RF → DM	59	1.7 (1.01–2.42)	2.6 (2.21–4.09)
LF/RF + DM	38	1.1 (0.51–1.56)	2.5 (1.54–2.81)

NPC: nasopharyngeal carcinoma; RT: radiotherapy, OS: overall survival; 95% CI: 95% confidence interval; DM: distant metastases; LF/RF: local and/or regional (neck) failure; LF/RF → DM: local and/or regional failure preceded the diagnosis of distant metastases by > 2 months; LF/RF + DM: local and/or regional failure occurred within 2 months of the diagnosis of distant metastases or after the diagnosis of distant metastases.

[a] Inadequate number of events beyond the median.

Time Course of Distant Failure in Different Patient Subsets

The time course for distant failure in different subsets of patients is shown in Table 2 and illustrated by the Kaplan–Meier overall survival curves in Figures 1 and 2. There appeared to be marked heterogeneity with regard to the overall survival among the patients with metastatic failure at different sites (Table 2) (Fig. 2). In particular, patients with lung metastasis alone had a median overall survival of 3.9 years, which is significantly longer than the median overall survival reported for other sites of pure DM ($P < 0.0001$ by the log-rank test). Lung metastasis also was associated with a significantly longer median time interval from primary radiotherapy to metastasis compared with that of DM occurring at other sites ($P = 0.0034$)

For the 97 patients with both DM and LF/RF during their course of disease, there was a trend toward a longer median time interval between primary radiotherapy and first DM in the LF/RF → DM group compared with the LF/RF + DM group (1.7 years vs. 1.1 years; $P = 0.073$) (Table 2) (Fig. 1). However, there was no significant difference noted with regard to the overall survival between the L/R → DM group and the L/R + DM group ($P = 0.13$, log-rank test) (Fig. 1). The overall survival curve of the L/R + DM group also was found to largely overlap with that of the pure DM group.

The Independent Prognostic Significance of Pure Lung Metastasis

The baseline clinical characteristics of the 41 patients with pure lung metastasis were compared with that of

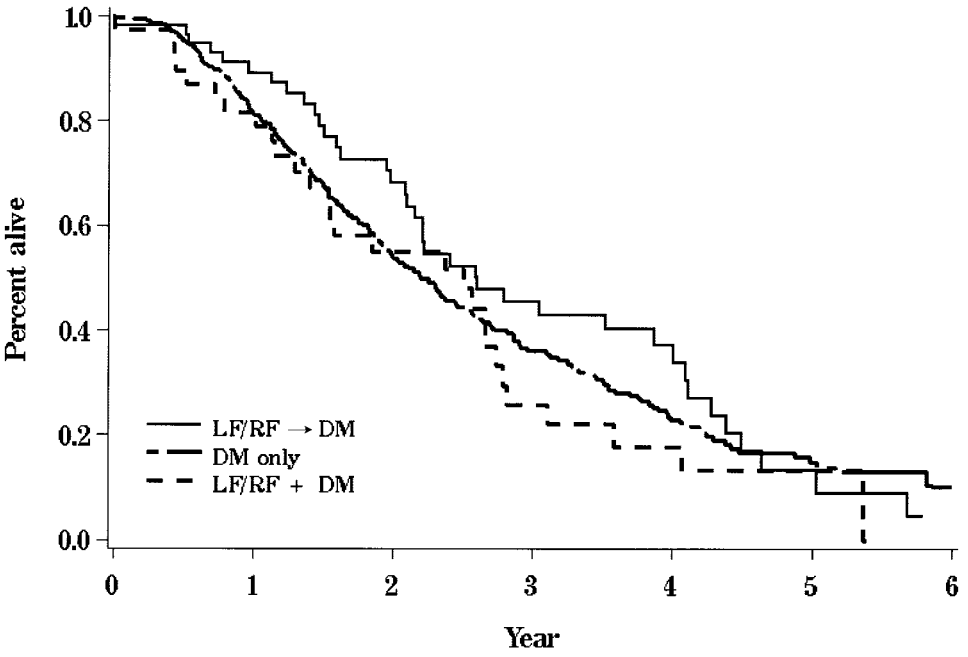

FIGURE 1. Kaplan–Meier overall survival curve for the different patterns of distant metastases (DM) in nasopharyngeal carcinoma. DM only: distant metastases without locoregional failure; LF/RF → DM: local and/or regional failure preceding distant metastases; LF/RF + DM: local and/or regional failure accompanied by distant metastases.

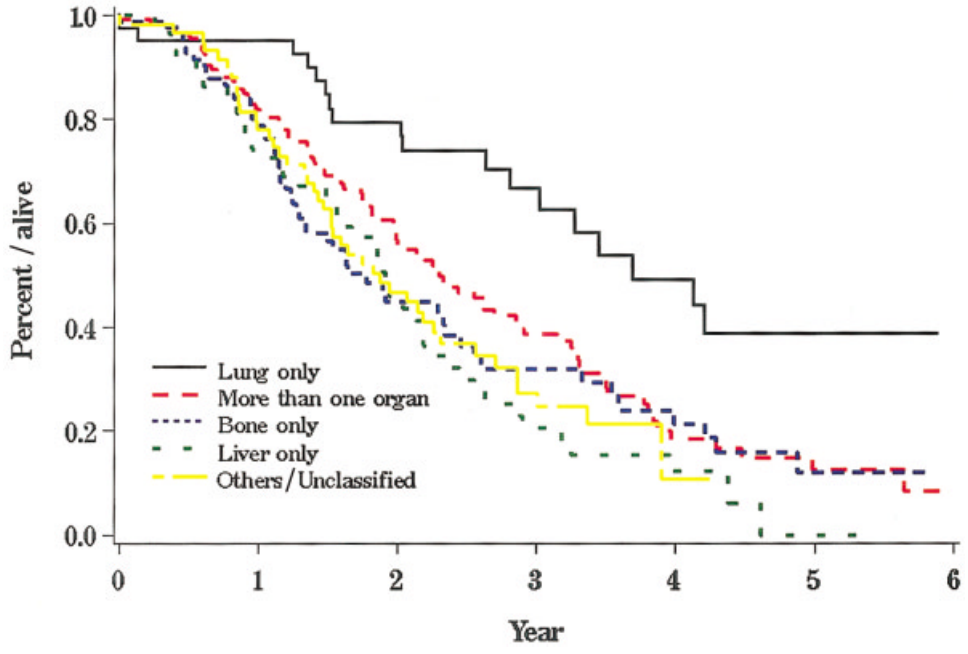

FIGURE 2. Kaplan–Meier overall survival curve for pure distant metastases stratified by metastatic site(s).

the entire cohort, and no significant difference was found (data not shown). To confirm the independent prognostic significance in the overall survival of this group, a Cox regression model was constructed and included all the baseline clinical parameters. The overall survival for this group with pure lung metastasis remained highly significant ($P = 0.0003$), even after adjusting for the other significant prognostic factors of overall survival (Table 3).

Predictive Factors of DM

The potential clinical characteristics at the time of primary diagnosis that may be predictive of the subsequent risk of DM were analyzed by both univariate (Table 4) and multivariate models (Table 5). These factors also had been analyzed across the different subgroups of DM. The significant predictive factors identified were fairly consistent in the different subgroups of DM. In summary, UICC N classification was

TABLE 3
Cox Regression Model: OS of Pure Lung Metastasis versus Non lung Metastasis, Adjusted for Other Significant Prognostic Factors

Factors	*P* value	HR	95% CI for HR
Age	0.025	1.01	1.002–1.02
Histology	0.012	1.28	1.06–1.56
UICC T classification	0.026	1.16	1.02–1.32
UICC N classification	< 0.0001	1.49	1.31–1.71
Lung metastasis	0.0003	0.41	0.25–0.66

OS: overall survival; HR: hazards ratio; 95% CI: 95% confidence interval; UICC: International Union Against Cancer.

found to be the strongest independent predictor of DM, followed by UICC T classification. Advanced age and male gender also were found to be significant independent risk factors for DM.

DISCUSSION

The current study reflects the clinical course of distant metastatic disease in a large cohort of NPC patients treated in the contemporary era. With the prospect of further improvement in local control with the increasing application of three-dimensional high-precision radiotherapy, distant failure is expected to become an even more outstanding problem. This point is well exemplified by recent studies that reported excellent local control in patients with advanced stage disease with the use of concomitant radiotherapy and chemotherapy[12] or intensity-modulated radiotherapy with or without chemotherapy.[1] Both studies had consistently demonstrated the increased burden of distant failure in NPC patients despite the achievement of excellent local control.

In the current study, we demonstrated a marked heterogeneity in the time course and survival in different metastatic sites for NPC patients who developed DM. In particular, patients with lung metastases alone appeared to belong to a distinctive group with a good prognosis and both a longer progression-free survival and overall survival. However, to our knowledge, the precise predictive factor for this prognostic group cannot be identified based on the available clinical parameters. We postulate that it may be associated with a unique biologic behavior of NPC in this particular group. The future study of molecular markers in NPC should aim to identify this significant prognostic group.

In a recent report that proposed a prognostic index score to predict survival in patients with metastatic NPC, the authors identified both liver metastasis and lung metastasis, among others, as independent and significant negative prognostic factors for metastatic survival.[13] The findings are in contrast to those of an earlier report from our group that suggested that although liver metastasis was associated with a shorter metastatic survival, patients with lung metastasis had a significantly longer metastatic survival.[3] The discrepancies between these reports and the results of the current study are likely the result of the different methods used to assess the survival outcome in patients with metastatic NPC. The previous reports all examined metastatic survival (defined as the time from the first diagnosis of DM to the time of death), whereas in the current study, we examined overall survival (calculated from the first day of primary radiotherapy to the time of death). We believe that overall survival is a more solid and appropriate outcome measure for the current study, when considering the commonly held view that DM actually originate from micrometastases that already are present at the time of primary radiotherapy treatment, and are an integral part of the disease at the time of first diagnosis. Conversely, the definition of metastatic survival is influenced by the time of clinical diagnosis of DM. The definition of this time point tends to be influenced by the interval between follow-up visits as well as the site of metastasis. Without routine surveillance imaging for DM, skeletal metastases may be more amenable to detection by clinical symptoms at an earlier stage of its natural history compared with pulmonary and hepatic metastases. Furthermore, the duration of metastatic survival also depends on the disease-free interval (DFI), which would again be heavily influenced by the primary treatment given. It is our opinion that the use of overall survival (DFI + metastatic survival) as the outcome measure will minimize these potential biases.

The natural history and management of metastatic NPC has long been an area of controversy. DM in patients with NPC have been conventionally regarded as incurable and the aim of treatment has largely been palliative. This view found support from previous experience in treating head and neck carcinoma at other sites, and observations from the historic reports concerning DM in patients with NPC. The literature had consistently reported a high rate of DM in patients with NPC, and poor survival after the diagnosis of metastasis. The reported median survival after the diagnosis of metastasis ranged from 5–11 months.[3,13–17] However, the experience from our center[3,18] and from other investigators in the French[5] and Canadian[6] series all suggested that a small proportion of patients with metastatic NPC who were treated with aggressive chemotherapy achieved long-term disease-free survival, suggesting the curative potential of chemotherapy, at least in a small subset of patients with

TABLE 4
Predictive Factors of Distant Metastases: Univariate Analysis

	Pure DM		LF/RF + DM		LF/RF → DM		Pure DM: lung only		Pure DM: non lung	
Factors	**HR**	***P* value**	**HR**	***P* value**	**HR**	***P* value**	**HR**	***P* value**	**HR**	***P* value**
Age	1.02	< 0.0001	0.99	0.46	1.00	0.78	1.03	0.0081	1.01	0.0011
Gender	0.67	0.0011	0.73	0.40	0.84	0.55	0.68	0.30	0.67	0.0021
Histology	0.98	0.83	0.45	0.019	1.08	0.66	0.96	0.86	0.99	0.87
UICC T classification	1.40	< 0.0001	1.53	0.0086	1.13	0.38	1.20	0.26	1.42	< 0.0001
UICC N classification	1.72	< 0.0001	1.99	< 0.0001	1.60	0.0003	1.39	0.036	1.77	< 0.0001

DM: distant metastases; LF/RF + DM: local and/or regional failure occurred within 2 months of the diagnosis of distant metastases or after the diagnosis of distant metastases; LF/RF → DM: local and/or regional failure preceded the diagnosis of distant metastases by > 2 months; HR: hazards ratio; UICC: International Union against Cancer.

TABLE 5
Predictive Factors of Distant Metastases: Multivariate Analysis

Factors	***P* value**	**HR**	**95% CI for HR**
Pure DM			
UICC N classification	< 0.0001	1.67	1.51–1.84
UICC T classification	< 0.0001	1.29	1.16–1.43
Age	< 0.0001	1.02	1.01–1.02
Gender	0.012	0.73	0.57–0.93
LF/RF + DM			
UICC N classification	< 0.0001	1.95	1.43–2.65
UICC T classification	0.017	1.48	1.07–2.04
LF/RF → DM			
UICC N classification	0.0003	1.60	1.24–2.06
Pure DM − lung			
Age	0.0059	1.03	1.01–1.06
Pure DM − non lung			
UICC N classification	< 0.0001	1.71	1.54–1.90
UICC T classification	< 0.0001	1.31	1.17–1.47
Age	0.0011	1.01	1.01–1.02
Gender	0.019	0.73	0.57–0.95

HR: hazards ratio; 95% CI: 95% confidence interval; DM: distant metastases; UICC: International Union against cancer; LF/RF + DM: local and/or regional failure occurred within 2 months of the diagnosis of the diagnosis of distant metastases or after the diagnosis of distant metastases; LF/RF → DM: local and/or regional failure preceded the diagnosis of distant metastases by > 2 months.

metastatic NPC.[4] We recommend an aggressive approach to managing metastatic NPC patients with a good performance status (especially if the metastasis is confined to the intrathoracic site), in whom long-term survival is a realistic goal after multimodality treatment.

Locoregional recurrence already has been recognized as an independent risk factor for DM in NPC patients, after N classification and T classification.[19] It also has been postulated that in patients whose DM are preceded by and/or accompanied by locoregional recurrence, the uncontrolled locoregional disease might serve as the origin of DM whereas DM occurring in the absence of locoregional recurrence may originate from occult disseminations at the time of primary radiotherapy.[3] Irrespective of the speculations concerning the source of the metastatic cells, the results of the current study demonstrated that the overall survival rate for patients with DM is not significantly different regardless of whether these DM were associated with locoregional recurrence. Furthermore, in those patients with both locoregional recurrence and DM, the overall survival was not found to be significantly altered despite the different management of the locoregional disease in the L/R → DM group (in whom aggressive salvage therapy would be given at the time of the identification of locoregional recurrence before the emergence of DM) compared with the L/R + DM group (in whom treatment was of palliative intent).

The results of the current study support previous reports that the incidence of DM after locoregional salvage therapy was significant (range, 20–34%) and as such, is the major determinant in predicting the overall survival of these patients.[20,21] An earlier study from the Radiation Therapy Oncology Group (RTOG) head and neck database also reported that tumors of the hypopharynx and nasopharynx had a higher probability of micrometastatic dissemination at the time of initial diagnosis, and until effective methods to treat disseminated disease were developed, the effect of local control on survival would not be discerned readily.[22] Future research should aim to identify the subgroup of patients at high risk for DM after successful locoregional salvage therapy. This group should be investigated by incorporating systemic therapy into their locoregional treatment, not only for the enhancement of local control, but also, more important, for eradicating microscopic metastasis to improve their overall survival. The recent development in high-sensitivity tumor markers, such as circulating plasma Epstein–Barr virus DNA, would be useful to identify residual disease after radiotherapy.[23]

The current study also confirmed the significant predictive factors for DM, namely advanced UICC N-

classified and T-classified disease, which is in keeping with previous reports from our group and others in the literature.[9,17,24,25] We also reported advanced age and male gender to be independent, significant risk factors for DM. Future studies should target patients with advanced UICC N-classified and T-classified tumors to test new strategies of systemic therapy to combat the risk of distant failure.

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