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Analysis of intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma

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Abstract

The present study aimed to retrospectively analyze the survival outcomes and prognostic factors for patients with nasopharyngeal carcinoma (NPC) receiving intensity-modulated radiotherapy (IMRT).

Clinical data was collected from 691 patients with NPC receiving IMRT from January 2009 to August 2015. A survival analysis was performed and prognostic factors were analyzed using the Kaplan–Meier method, the Cox proportional hazards regression model, and the log-rank test.

The median follow-up time was 62.8 months. Sixty-three patients experienced relapse, 44 cases (70%) of which occurred within 3 years. Six cases (9.5%) remained in remission for over 5 years. Seventy-two patients developed metastasis, 63 cases (87.5%) of which occurred within 3 years and only 1 case occurred after 5 years (1.3%). Five-year disease special survival (DSS), progression free survival, locoregional recurrence free survival, and distant metastasis free survival were 86.5%, 82.5%, 90.7%, and 89.4%, respectively in patients with NPC. Patients with stage III NPC with and without induction chemotherapy had 5-year DSS rates of 95.8% and 89.3%, respectively ($P = .00$). Patients with stage IVa NPC with and without induction chemotherapy had 5-year DSS rates of 73.1% and 68.9%, respectively ($P = .04$). The 5-year DSS rates of patients with stage III with or without concurrent chemotherapy were 92.8% and 85.5%, respectively ($P = .04$). The 5-year DSS rates of patients with stage IV with or without concurrent chemotherapy were 72.7% and 53.0% ($P = .02$).

IMRT improves the survival rate of patients with NPC. Recurrence and metastasis mainly occur within 2 to 3 years after radiotherapy. Induction and concurrent chemotherapy improve the 5-year DSS of patients with locally advanced NPC.

Abbreviations: CCRT = concurrent chemoradiotherapy, DMFS = distant metastasis free survival, DSS = disease-special survival, IC = induction chemotherapy, IMRT = intensity-modulated radiotherapy, LRFS = locoregional recurrence free survival, NPC = nasopharyngeal carcinoma, OS = overall survival, PFS = progression free survival.

Keywords: concurrent chemotherapy, intensity-modulated radiotherapy, nasopharyngeal carcinoma, survival analysis

1. Introduction

Nasopharyngeal carcinoma (NPC) has a distinct geographical distribution. Guangdong is one of the remarkable endemic areas with an annual morbidity of 30 to 40/100,000 compared with 0.5 to 1/100,000 in America.[1,2] There are 3 main subtypes of NPC: keratinizing squamous cell NPC, non-keratinizing squamous cell NPC, and basaloid squamous cell NPC according to the World Health Organization. The non-keratinizing squamous cell NPC is the dominating pathological subtype associated with Epstein–Barr virus infection among the endemic areas of south and east Asia, which can be divided into differentiated and undifferentiated tumors that are sensitive to radiation.[3,4] Radiotherapy is the mainstay therapy for non-metastatic disease and has advanced from conventional 2-dimensional or 3-dimensional radiotherapy to intensity-modulated radiotherapy (IMRT). In the last 20 years, IMRT has allowed an increase in the dose of radiation applied to tumor lesions, while reducing radiotherapy-related toxicity to surrounding organs. Previous studies have shown that IMRT reduced the 5-year LRFS compared with conventional techniques,[5–7] and patients with NPC receiving IMRT had a 5-year overall survival (OS) of 75% to 83%, a DSS of 79% to 85%, a LRFS of 90% to 95%, and DMFS of 85% to 90%.

Treatments for NPC are based on the stage of the disease. While patients with stage I and II NPC usually receive concurrent chemoradiotherapy (CCRT), patients with stage III and IVa NPC

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undergo induction chemotherapy (IC) or adjuvant chemotherapy combined with CCRT. A number of randomized trials have demonstrated the survival benefit of CCRT with IC or adjuvant chemotherapy in patients with NPC, and survival benefits have been proved through indirect comparison between them. Compared with adjuvant chemotherapy, IC has evident advantages in producing better tolerance and earlier eradication of micro-metastase.[8–12] The related adverse events, especially hematologic toxicity and radiation-induced oral mucositis, may require extra attention. Meanwhile, it is reported that anti-epidermal growth factor receptor (EGFR) agents, such as cetuximab and nimotuzumab, when used in combination with IC or CCRT, improve of progression-free survival (PFS), DMFS, and OS.[13–15]

High programmed cell death ligand-1(PD-L1) expression is observed in up to 90% of tumor cell in NPC.[3] Recently, immune checkpoint blockade therapy has undergone breakthroughs in NPC immunotherapy as objective response ranging from 20% to 30%, 1-year OS ranging from 59% to 63%, 1-year PFS ranging from 19% to 33% after monotherapy were reported.[16] In combination trials, the objective response can increase to 91% and 1-year PFS can increase to 61%.[17] The immunotherapy is mainly focused on recurrence and metastasis of NPC and there is a little data about immunotherapy combined with radiotherapy for the treatment of NPC. But there are some phase 2 or 3 randomized clinical trials about immunotherapy combined with concurrent chemo-radiotherapy for high-risk NPC undergoing in Sun Yat-Sen University Cancer Center (NCT03984357, NCT03925090, NCT03427827, NCT03700476).

This study retrospectively analyzed clinical data from 691 patients with NPC receiving IMRT at Shenzhen People's Hospital and explored the failure patterns with the aim of providing a pivotal prognostic reference for future clinical research.

2. Methods

2.1. Patients and data collection

This is a retrospective study and the ethical approval was not necessary. A total of 691 newly diagnosed patients with non-metastatic NPC at Shenzhen People's Hospital between January 2009 and June 2015 were enrolled. The inclusion criteria were as follows:

(1) patients with NPC and nasopharyngeal mass biopsies that were histologically classified as keratinized or non-keratinized and imaging-confirmed absence of distant metastasis;
(2) absence of other concurrent malignant tumors;
(3) patients receiving IMRT treatment. The 6th-edition classification from the Union for International Cancer Control was used for diagnosis.

2.2. Treatments

The target volume delineation for patients receiving IMRT was determined using guidelines 50 and 62 of the International Commission on Radiation Units. The prescribed dose was 68 to 70Gy to the gross target volume of the nasopharynx, 64 to 68Gy to cervical lymph node metastasis, 60Gy to high-risk clinical target volume, and 54Gy to low-risk clinical target volume, each with 33 fractions. For patients receiving induction or adjuvant chemotherapy, these regimens were administered every 21 days and a total of 2 to 3 cycles were applied prior or posterior to radiotherapy. The regimens were as follows:

(1) cisplatin, fluorouracil, and docetaxel (TPF) regimen, 60 mg/m^2/dl paclitaxel and cisplatin and 600 mg/m^2/d1 to 5 fluorouracil;
(2) cisplatin and fluorouracil (PF) regimen, 80 mg/m^2/dl cisplatin and 800 mg/m^2/d1 to 5 fluorouracil;
(3) cisplatin and docetaxel (TP) regimen, 80 mg/m^2/d1 paclitaxel and cisplatin. Cisplatin as a single agent was administered on days 2 and 23 during radiotherapy for concurrent chemotherapy, whereas nimotuzumab was administered to patients with stage III to IVa NPC for targeted therapy at a dose of 200 mg once per week.

2.3. Follow up and evaluation criteria

Patients were asked to return to our clinic every 3 months for nasopharyngeal and neck magnetic resonance imaging in the first 2 years. This follow up was gradually decreased to every 6 months in the following 3 years and to once annually for patients without observed relapse or metastasis. Patients received at least 1 comprehensive check annually including nasal endoscopy, chest-abdomen computed tomography, and an emission computed tomography bone scan or whole-body positron emission tomography.

Several endpoints were used in this study. The definition of endpoint OS was the time from diagnosis to death of any cause, and loss to follow up was marked as censored data. DSS was defined as the time from diagnosis to death from NPC, and loss to follow up or death from other causes were marked as censored data. In addition, PFS was defined as the time from diagnosis to locoregional or distant failure, while LRFS was defined as the time from diagnosis to locoregional failure. DMFS was defined as the time from diagnosis to distant failure, and loss to follow up or death from any cause was marked as censored data.

2.4. Statistical analysis

Survival curves were created using the Kaplan–Meier method and compared with the help of the log-rank test. Cox multivariate regression modeling was used to evaluate the prognostic factors. SPSS 22.0 software (IBM.com) was used for statistical analysis where $P < .05$ was considered statistically significant.

3. Results

3.1. Demographic and pathological features

A total of 509 males and 182 females were enrolled in the study with a median age of 44 years (15–80 years) and a male to female ratio of 2.8 (Table 1). Twenty-seven (3.9%) patients were identified as stage I, and 118 (17.1%), 343 (49.6%), and 203 (29.4%) patients were identified as stage II, III, and IVa, respectively. Of the 691 patients receiving IMRT, 238 (34.4%) and 458 (66.3%) patients received induction and concurrent chemotherapy, respectively, while 73 (10.6%) and 137 (19.8%) patients received adjuvant chemotherapy and targeted therapy, respectively.

3.2. Survival

The follow up ended on June 30th, 2018 with a median of 62.8 months. Sixty-three patients experienced relapse, of which

Table 1

Characteristics of 691 patients with nasopharyngeal carcinoma.

Characteristics	Number	%
Gender		
Male	509	73.7
Female	182	26.3
Age		
< 50 yr	447	64.7
≥ 50 yr	244	35.3
T stage		
T1	132	19.1
T2	237	34.3
T3	209	30.2
T4	113	16.4
N stage		
N0	69	10.0
N1	169	24.5
N2	335	48.5
N3	118	17.1
TNM stage		
I	27	3.9
II	118	17.1
III	343	49.6
IVa	203	29.4
Induction chemotherapy		
Yes	238	34.4
No	453	65.6
Concurrent chemotherapy		26.3
Yes	458	66.3
No	233	33.7
Adjuvant chemotherapy		
Yes	73	10.6
No	618	89.4
Targeted therapy		
Yes	137	19.8
No	554	80.2
Recurrence		
Yes	63	9.1
No	628	90.9
Metastasis		
No	619	89.6
Lung	12	1.7
Liver	14	2.0
Bone	12	1.7
Multiple*	34	4.9

* Metastasis observed in 2 or more locations.
TNM = tumor-node-metastasis

44 (69.8%) presented with nasopharyngeal recurrence, 17 (27.0%) presented with locoregional lymph node recurrence, and 2 (3.2%) presented with combined recurrence (Table 1). Recurrence was observed 4 to 91 months after radiotherapy with 70% of patients experiencing relapse within 3 years, 30% of patients experiencing relapse beyond 3 years, and 9.5% of patients remaining in remission for 5 years before experiencing relapse.

Of the 72 patients with distant metastases, 34 (47.2%), 14 (16.7%), and 12 patients had multiple metastases, liver metastasis, and lung and bone metastases, respectively. It is worth highlighting that 10 patients experienced distant metastasis and relapse simultaneously. Distant metastasis was observed 3 to 66 months after radiotherapy; 87.5% of distant metastases occurred in the first 3 years and 12.5% of distant metastases occurred beyond 3 years. Only 1.3% of patients experienced distant failure after 5 years (data not shown).

Table 2

Treatment efficacy in patients with different stages of nasopharyngeal carcinoma.

Stage	5-yr OS	5-yr DSS	5-yr PFS	5-yr LRFS	5-yr DMFS
Overall	85.8%	86.5%	82.5%	90.7%	89.4%
I	95.8%	100%	100%	100%	100%
II	96.5%	96.5%	95.9%	99.2%	96.0%
III	91.4%	91.4%	87.0%	93.5%	92.7%
IVa	69.7%	69.7%	64.8%	83.4%	76.1%

OS = overall survival, DSS = disease-specific survival, PFS = progress-free survival, LRFS = local recurrence-free survival, DMFS = distant metastasis-free survival.

To better understand the survival and prognostic patterns of patients with NPC, we performed a survival analysis based on different study endpoints. For all patients in the study, 5-year OS, DSS, PFS, LRFS, and DMFS were 85.8%, 86.5%, 82.5%, 90.7%, and 89.4%, respectively. Patients with stage I NPC exhibited an OS as high as 95.8%, and 100% DSS, PFS, LRFS, and DMFS. Patients with stage II and III NPC showed lower but comparable survival rates at each endpoint (OS: 96.5% vs 91.1%; DSS: 96.5% vs 91.4%; PFS: 95.9% vs 87.0%; LRFS: 99.2% vs 93.5%; DMFS: 96.0% vs 92.7%, respectively). As anticipated, patients with stage IV NPC had relatively low OS (69.7%), DSS (69.7%), PFS (64.8%), LRFS (83.4%), and DMFS (76.1%) rates (Table 2 vs Fig. 1-ABCD).

3.3. Prognostic factor analysis

To assess the factors influencing the prognosis of patients with NPC, a backward selection in the Cox regression model was used, and gender, age, T stage, N stage, and type of chemotherapy were the variables. We showed that gender, T stage, and N stage independently affected DSS, PFS, LRFS, and DMFS. In addition, patients receiving CCRT had significantly higher OS, DSS, and LRFS rates (Table 3).

3.4. The effect of chemotherapy on the efficacy of treatment of regional advanced NPC

To examine whether different chemotherapy regimens influence disease onset, we compared 5-year DSS in patients with stage III and IVa NPC receiving IC, CCRT, and targeted therapy. While targeted therapy exerted no effect on patient prognosis, IC and CCRT significantly improved the DSS of patients with stage III and IVa NPC, indicating better treatment options for patients with regional advanced NPC (Table 4). Our data also showed an overall poor prognosis for patients with stage IVa NPC with a DSS of < 73.1%, despite the chemotherapy regimen being administered.

3.5. Second primary malignancy and distant severe complications

We observed a second primary malignancy in 17 patients during the follow-up period with a median development time of 60 months (36–83 months). Four of the 17 patients developed lung cancer and 2 patients developed each of liver cancer, gastric carcinoma, and glioma. The remaining 7 patients developed osteosarcoma of the maxilla (n = 1), esophageal cancer (n = 1), gingival carcinoma (n = 1), tongue cancer (n = 1), laryngeal cancer (n = 1), colon cancer (n = 1), or bladder cancer (n = 1; data not

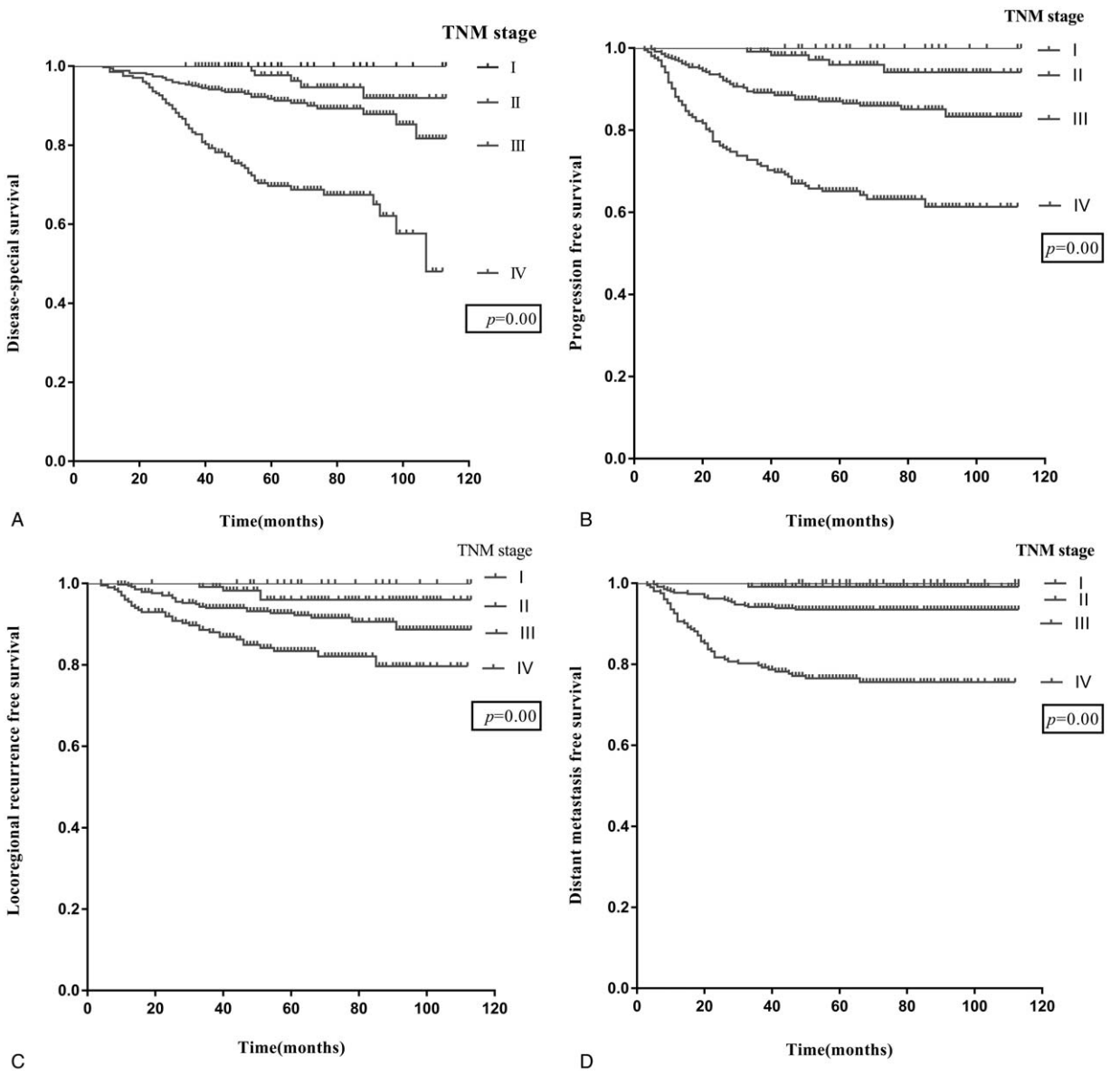

Figure 1. Survival analysis of 691 patients with nasopharyngeal carcinoma (NPC). A. Disease-special survival of 691 patients with NPC; B. Progression free survival of 691 patients with NPC; C. Locoregional recurrence free survival of 691 patients with NPC; D. Distant metastasis free survival of 691 patients with NPC.

shown). All patients died despite no recurrence or metastasis. In addition to the aforementioned 17 subjects, we also observed distant severe complications in 8 subjects. Four subjects experienced damage to the posterior cranial nerve, 2 patients had gross nasopharyngeal bleeding, and 2 patients experienced carotid artery rupture.

A total of 109 deaths occurred during the study. One hundred two subjects died from tumor or tumor-related complications and 7 died from non-tumor causes (2 from severe lung infection, 2 from cerebral infarction, 1 from myocardial infarction, 1 from depression, and 1 from femoral fracture).

4. Discussion

IMRT has replaced conventional radiation therapy and has been the main therapeutic technique for NPC since the beginning of the 21st century due to its distinct advantages on dose control and target delineation.[18–21] IC and CCRT is significantly associated with better locoregional control and OS.[11,22] Anti-EGFR agents in conjunction with CCRT are associated with significantly increased OS and DFS rates, as well as improved DMFS. With this approach, the main adverse events are mild skin reactions and mucositis.[23–25] Recent progress in tumor immunotherapy make it a promising therapeutic approach for advanced NPC, but strong evidence for tumor immunotherapy in early NPC is lacking.

In this study, we further confirmed that IMRT can increase the survival of patients with NPC. We showed that the 5-year OS, DSS, PFS, LRFS, and DMFS rates were 85.8%, 86.5%, 82.5%, 90.7%, and 89.4%, respectively. We also showed that 5-year LRFS and DMFS rates in patients with stage I NPC were 100% and 100%, respectively; stage II NPC were 99.2% and 96.0%,

Table 3

Prognostic factors analysis.

Endpoints	Variables	HR	95%CI	P
OS	Gender	2.03	1.21–3.42	.00
	Age	1.84	1.25–2.70	.00
	T stage	1.73	1.39–2.13	.00
	N stage	2.09	1.61–2.72	.00
	Concurrent chemotherapy	0.62	0.40–0.95	.02
DSS	Gender	2.41	1.37–4.25	.00
	Age	1.77	1.19–2.63	.00
	T stage	1.88	1.51–2.34	.00
	N stage	2.20	1.68–2.89	.00
	Concurrent chemotherapy	0.61	0.39–0.95	.03
PFS	Gender	1.88	1.18–3.02	.00
	T stage	1.71	1.41–2.08	.00
	N stage	2.09	1.64–2.65	.00
LRFS	Gender	2.39	1.18–4.85	.02
	T stage	2.22	1.66–2.95	.00
	N stage	1.55	1.11–2.15	.01
	Concurrent chemotherapy	0.50	0.29–0.86	.01
DMFS	Gender	2.27	1.16–4.42	.02
	T stage	1.49	1.15–1.93	.00
	N stage	3.22	2.26–4.57	.00

Female patients, age less than 50 years with T1 and N0 nasopharyngeal carcinoma, without receiving concurrent chemotherapy were used as reference group.

OS = overall survival, DSS = disease-specific survival, PFS = progress-free survival, LRFS = local recurrence-free survival, DMFS = distant metastasis-free survival.

respectively; stage III NPC were 93.5% and 92.7%, respectively; and stage IVa NPC were 83.4% and 76.1%, respectively. These observations are in agreement with previous studies. Setton et al reported 3-/5-year actuarial OS, LRFS, and DMFS rates of 87%/74%, 92%/83%, and 86%/83%, respectively, in 177 consecutive newly diagnosed patients with non-metastatic NPC treated with definitive IMRT between 1998 and 2011.[26] Meanwhile, we reported 63 and 72 cases of recurrence and metastasis, respectively, during the follow-up period, during which patients experienced relapse within 4 to 91 months and metastasis within 3 to 66 months of receiving radiation therapy. Although 70% of relapses occurred within 3 months and up to 9.5% of patients remained in remission for 5 years, 87% of metastases developed within 3 years and only 1.3% occurred after 5 years. Setton et al also showed that more than half of the observed local relapses occurred after 2 years. Our study demonstrated that patients with NPC typically experience recurrence and metastasis within 2 to 3 years of receiving radiotherapy, which is a common characteristic also reported in other studies. The failure pattern of NPC is distinct from that of carcinomas arising from other head and neck sites. These findings raise the possibility that patients with NPC may benefit from close follow up during post-treatment years 3 to 5.

Table 4

The effect of different chemotherapy on 5-years disease-specific survival in patients with regional advanced nasopharyngeal carcinoma.

Stage	Treatment	Number	5-year DSS	P
III	Induction chemotherapy			
	Yes	121	95.8%	.00
	No	222	89.3%	
	Concurrent chemotherapy			
	Yes	260	92.8%	.04
	No	83	85.5%	
	Targeted therapy			
	Yes	75	93.1%	.29
	No	268	91.1%	
IVa	Induction chemotherapy			
	Yes	112	73.1%	.04
	No	91	68.9%	
	Concurrent chemotherapy			
	Yes	172	72.7%	.02
	No	31	53.0%	
	Targeted therapy			
	Yes	49	63.7%	.17
	No	154	71.6%	

The comparison among groups were statistically significant, $P < .05$.

DSS = disease-specific survival.

Our study suggests that, when combined with the tumor-node-metastasis classification, the T and N stages of NPC are precise prognostic factors, as no crossings were observed in the survival curves from our multivariate analysis of prognosis. The incidences of recurrence and metastasis observed in this study were 73.0% and 22.2%, respectively, in patients with stage T3 and T4; and 65.0% and 47.2%, respectively, in patients with stage N3 (data not shown). Sun et al reported 5-year LRFS rates of 100.0%, 96.0%, 90.4%, and 83.3% in patients with stage T1, T2, T3, and T4 NPC, respectively, as well as 5-year DMFS rates of 96.1%, 85.6%, 73.7%, and 62.1% in patients with stage N0, N1, N2, and N3 NPC, respectively.[27] In accordance with their findings, we found that the 5-year LRFS rates in patients with stage T1, T2, T3, and T4 disease were 98.3%, 96.0%, 90.5%, and 79.0%, respectively ($P < .00$). Furthermore, the 5-year DMFS rates in patients with stage N0, N1, N2, and N3 were 100%, 97.0%, 90.0%, and 70.9%, respectively ($P = .00$). The T and N stages are associated with LRFS and DMFS, as demonstrated by previous research.[28,29] Xu et al demonstrated that IC plus CCRT has no significant survival benefit for patients with locoregionally advanced NPC but results in significant metastasis-free survival efficacy in T3 to 4/N0 to 1 populations.[30] However, more and more hard evidence has confirmed that a combination of IC and CCRT is a promising treatment strategy for NPC. We also reported a higher 5-year DSS in patients with stage III and IVa NPC receiving concurrent or IC (Table 4). Data on adverse events was absent, but previous studies support that this treatment combination could be tolerated by patients with NPC.[8–10] Seventeen subjects (2.46%) developed a second primary cancer during the follow-up period. Chiu et al reported an incidence of 1.54% for second primary cancers in a 10-year retrospective study involving 905 subjects.[31] These second primary cancers included osteosarcoma, parotid carcinoma, and hard palate cancer; thus, these cancers were mainly located within the irradiation area. In our study, second primary cancerous tumors developed in the proximity of the nasopharynx and lung (64.7%; 11/17) in areas within or adjacent to the irradiation field. The main cause of second primary cancer remains unclear. Although it was not addressed in several large retrospective studies, the higher risk of developing tumors in the proximity of the radiation area suggests a need for suitable radiation doses and target volume delineation planning. The common procedure to reduce radiation-induced cancer is to control the dose of irradiation received by regional organs and restrict the scattering and leakage of radiation during treatment. Thus, it is pivotal for patients with advanced NPC to monitor the irradiated and adjacent areas for early detection of second primary tumors.

5. Conclusion

We achieved a treatment efficacy that was comparable with other large national medical institutions with distant metastasis being the main cause of treatment failure in patients with NPC. The tumor-node-metastasis classification is related to survival. While combining IC and concurrent chemotherapy with IMRT can improve 5-year DSS, the impact of targeted therapy on patients with advanced NPC requires further investigation. Finally, close monitoring and early detection of second primary tumors is pivotal as patients' survival times increase.

Author contributions

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