The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 52, Sep 2026
ISSN No. 2078-2101







Under the Patronage and Honoring of HRH Prince Saud bin Nayef bin Abdulaziz, Governor of the Eastern Province: Saudi Cancer Foundation Successfully Launches "AlSharqia Wardiyah 18"

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Efficacy of Volumetric Modulated Arc Therapy (VMAT) in Nasopharyngeal Carcinoma: A Retrospective Analysis.

Venkada Manickam Gurusamy[1], Palmira Caparrotti[1], Hissa Hussain Al–Abdulla[1], Saju Raveendran Divakar[1], Ghazia Shaik[1], Patsey Conway–Murray[1], Amna Rafi Vora[1], Muhammad Usman[1], Rabih Wafiq Hammoud[1], Noora Al–Hammadi[1].

[1] Department of Radiation Oncology, National Center for Cancer Care and Research (NCCCR), Hamad Medical Corporation, Doha, Qatar.

Abstract

Purpose: This retrospective study evaluates the efficacy of volumetric arc radiotherapy (VMAT) in NPC patients at a tertiary hospital in Qatar, serving a diverse population. The primary endpoint was loco–regional tumor control, while secondary endpoints included disease–free survival, overall survival and treatment–related toxicities.

Methods and materials: Patients older than 16 years who had T1 – T4N0 – 3M0 nasopharyngeal cancer and the WHO performance status of 0 or 1 were included. All patients received radiotherapy with or without chemotherapy as indicated. Initially, our institution policy was concurrent chemoradiotherapy (CCRT) followed by adjuvant chemotherapy for advanced stage disease. After the publication of randomized trials showing significant improvement in clinical results with induction chemotherapy followed by concurrent chemoradiation, our practice was changed accordingly.

Results: All 67 patients completed volumetric arc intensity–modulated radiotherapy and the overall median radiotherapy dose was 70 Gy (IQR 66 – 76 Gy). In total, 12 of 67 patients (17.9%) received CCRT alone and 52 of 67 patients (77.6%) received either induction chemotherapy or adjuvant chemotherapy. We recorded a total of 11 events of recurrence, distant metastasis or death in 8 of 67 patients (11.9%). Distant metastasis was seen in 6 of 67 patients (89.5%), and 3 of 67 patients (4.6%) had both locoregional failure and distant metastasis. For all patients, 3–year overall survival (OS), disease–free survival (DFS) and locoregional recurrence–free survival (LRRFS) were 98% (95% CI, 94.1 – 100%), 87.3% (95% CI, 78.6 – 97%) and 92.8% (95% CI, 86.1 – 99.9%), respectively.

Conclusion: Our analysis demonstrates that the combination of VMAT and chemotherapy achieves excellent long–term tumor control, with outcomes comparable to previously published data.

Introduction

Nasopharyngeal cancer (NPC) is a rare malignancy arising from squamous epithelium in the nasopharynx. The global age–standardized incidence rates were 2.2 per 100 000 in men and 0.8 in women in 2020 which accounted 96,371 and 36,983 new cases respectively [1]. NPC generally differs from other head and neck cancers in terms of epidemiological features, histopathological subtypes, treatment, and prognosis.

Nasopharyngeal carcinoma has a marked variation in geographic and racial distribution, being endemic in Southeast Asia southern China and North Africa but less common in Western countries [2]. More than 70% of newly diagnosed patients are classified to have locoregionally advanced disease, which is associated with unfavorable survival outcomes [3]

The treatment landscape of this aggressive malignant neoplasm has witnessed significant improvements in the last few decades. Locoregional control has substantially improved with combined use of intensity–modulated radiotherapy (IMRT) and chemotherapy while distant metastasis is now the main source of treatment failure[4,5]. Recently, satisfactory results have also been obtained with addition of induction chemotherapy (IC) to concurrent chemoradiotherapy (CCRT) [6,7].

Corresponding author: Venkada Manickam Gurusamy, Department of Radiation Oncology, National Center for Cancer Care and Research (NCCCR), Hamad Medical Corporation, Doha, Qatar.
E–mail: vgurusamy@hamad.qa

Importantly, the closest biological association of Epstein–Barr virus (EBV) infection in carcinogenesis has recently been established, which could be used to guide therapeutic decisions and prognosis evaluation in the clinic [8–10]. EBV positive NPC is usually infiltrated by lymphocytes in the tumor stroma therefore it is an attractive target for immunotherapy [11]. Several randomized trials are currently underway to evaluate therapeutic benefits of adding more potent immunotherapy such as anti–programmed death–1 (PD–1) antibody (e.g. NCT03427827, NCT03267498 and NCT03700476).

Nasopharyngeal cancer (NPC) remains a challenging malignancy, particularly in the Middle East, where demographic differences and limited data on treatment outcomes persist. This retrospective study evaluates the efficacy of volumetric arc radiotherapy (VMAT) with or without chemotherapy in NPC patients at a tertiary hospital in Qatar, serving a diverse population, including both local and expatriate patients, to provide valuable insights into regional clinical outcomes. Locoregional control of tumors treated with radiation was the primary outcome of this study. Secondary outcome measures were disease free survival and overall survival. Additional secondary endpoints were acute and late side effects associated with radiotherapy.

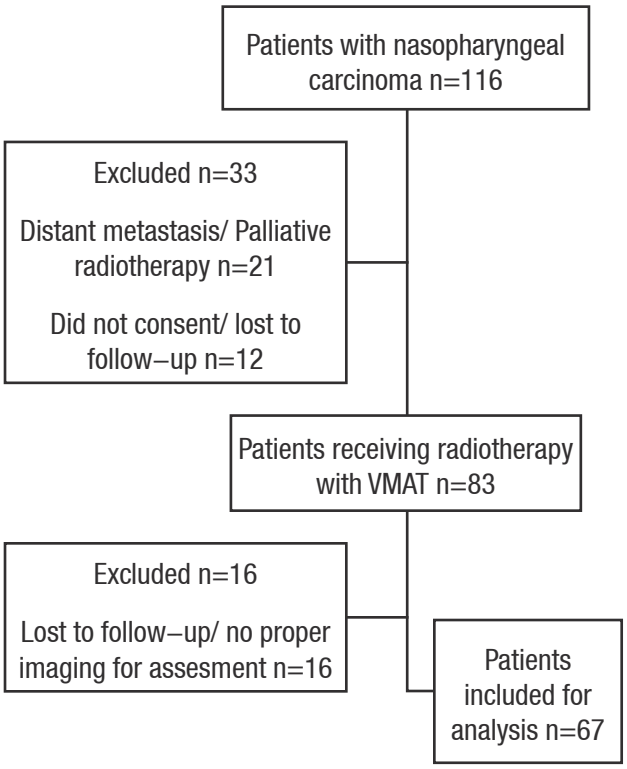


Figure 1: The consort flow diagram. VMAT – volumetric modulated arc therapy.

Methods and materials

Patients and treatment

This is a single–center retrospective analysis of nasopharyngeal carcinoma patients who received RT with or without chemotherapy. Initial review of the database at our institution from January 2015 to December 2023 identified 116 histology confirmed patients. Patients older than 16 years who had T1 – T4N0 – 3M0 nasopharyngeal cancer and the WHO performance status of 0 or 1 were eligible. Patients who lost to follow–up or postradiotherapy imaging were excluded, which resulted in 67 consecutive patients for analysis [Fig 1]. This study was reviewed and approved by our institute Medical Research Center. Informed consent for the study participation was not deemed necessary because of the retrospective nature of this study.

Essential pretreatment assessments were a complete patient history, physical examination, fiberoptic endoscopy, magnetic resonance imaging (MRI) of the nasopharynx and neck and systemic staging with positron emission tomography/computed tomography (PET/CT) scan or CT scan. Patients were staged according to the 8th AJCC staging system [12]. International guidelines were utilized to classify neck nodal stations [13]. Treatment strategies were made in the institution's multidisciplinary meetings as per our standard practice guidelines. All patients received radiotherapy with or without chemotherapy as indicated. Initially, our institution policy was concurrent chemoradiotherapy (CCRT) followed by adjuvant chemotherapy for advanced stage disease. After the publication of randomized trials showing significant improvement in clinical results with induction chemotherapy followed by CCRT, our practice was changed accordingly [14].

Eligible patients were offered either three cycles of docetaxel, cisplatin and fluorouracil (TPF) or gemcitabine with cisplatin induction chemotherapy followed by concurrent chemoradiotherapy at the discretion of the treating medical oncologist. CCRT patients received chemotherapy either every 3 weeks or weekly cisplatin. Adjuvant chemotherapy was cisplatin or carboplatin with fluorouracil.

Radiotherapy planning and daily imaging

All patients received volumetric modulated arc therapy (VMAT). After patients were positioned on the treatment couch in the treatment position as comfortably and reproducibly as possible, neck rests providing adequate support for the head and neck, a 5–point mask and appropriate knee rests were used for immobilization. After the CT simulation, patients underwent the dedicated MRI

simulation with a 1.5 Tesla GE Optima MR450w scanner in the treatment position, and T1 and T2 weighted axial scans were acquired. A PET/CT simulation scan was performed at the discretion if a diagnostic PET/CT was not available at the discretion of the treating radiation oncologist.

Gross tumor volume (GTV) included the primary tumor in the nasopharynx and the enlarged lymph nodes. Clinical target volume 70 (CTV 70) was defined as the gross tumor volume plus a 5 mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the high–risk sites of microscopic extension and the nasopharynx. CTV 59.4 was defined as the high–risk clinical target volume plus a 5 – 10 mm margin (2 – 3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the sites of microscopic extension, including skull base, clivus, sphenoid sinus, parapharyngeal space, pterygoid fossae, posterior parts of the nasal cavity, pterygopalatine fossae, retropharyngeal nodal regions, and the neck nodes from level IB to III [15]. CTV 54 included other elective neck nodal levels up to clavicles. In patients who received induction chemotherapy, CTV 70 and CTV 66 were contoured to cover post chemotherapy residual GTVand prechemotherapy GTVs respectively. The PTV was created with an expansion of 5 mm.

The prescription included in this study was 70 Gy, 66 Gy, 59.4 Gy and 54 Gy in 33 fractions with five daily fractions per week for 6 – 7 weeks; simultaneous integrated boost technique was used to obtain optimal dose painting at different dose levels. RapidArc IMRT plans were generated according to the International Commission on Radiation Units and Measurements (ICRU) report No. 83 and international guidelines standards [16]. Peer review of contours and chart review of radiotherapy treatment plans were routinely done during the study period.

The VMAT treatment was delivered with daily online image guidance. Kilovoltage (kV) orthogonal pairs or cone beam CT (CBCT) images were acquired before the radiation delivery and set–up errors were verified by the trained radiation therapists. Errors exceeding 1 mm in any of the cardinal directions corrected online before the treatment delivery.

Assessment/Follow–Up

All patients were assessed while on radiotherapy once weekly by the treating radiation oncologist. Follow–up evaluation included the assessment with fiberoptic endoscopy and imaging every 3 to 6 months for the first 2 years and yearly once thereafter at the discretion of the treating medical oncologist and head & neck surgeon. Acute and late toxicity data were collected using physician–completed electronic medical records. Grading of acute toxicity was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Clinical diagnosis of recurrence was accepted if classical changes were present with or without clinical symptoms on imaging methods. If imaging findings were equivocal, subsequent follow–up was used to confirm the disease progression. Salvage treatments including re–irradiation, chemotherapy, or surgery were offered in patients with relapse or persistent disease, in accordance with our standard practice.

Complete response was defined as complete disappearance of soft tissue mass in the local region and all cervical lymph nodes must have reduction in short axis to less than 10 mm. Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions with reference to the baseline. At least a 20% increase in the sum of diameters of target lesions (an absolute increase of at least 5 mm), or the appearance of one or more new lesions was defined as progressive disease. Stable disease was determined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease[17]. PET/CT scans were assed in compliance with the international guideline [18]

Statistics

Summary statistics for numerical data included the median with range or the mean with standard deviation (SD). The time–to–event data was described with Kaplan–Meier curves.

The primary endpoint was locoregional recurrence–free survival, which was calculated from the date of diagnosis to the date of locoregional failure or death from any cause, whichever occurred first.

Overall survival was calculated from date of diagnosis to death; disease–free survival as date of diagnosis to first locoregional or distant failure. Missing time–to–event data (due to loss to follow–up or no event observed at the time of predefined time of analysis) were censored. All the analyses were done with Jamovi ver. 2.3 (2022; https://www.jamovi.org).

Results

Sixty–seven consecutive patients who received radiotherapy for nasopharyngeal carcinoma between January 2015 and December 2023 were included for analysis. The patient demographic and treatment characteristics are shown in Table 1. The median patient age was 48 years (range, 16–80 years).

	All patients	
	n	%
Sex		
Male	58	86.6
Female	9	13.4
Endemic population		
Yes	37	55.2
No	30	44.8
Region		
Middle East	16	23.8
South East Asia	33	49.3
Africa	14	20.9
others	4	6.0
Symptoms		
Lymphadenopathy	38	56.7
Hearing abnormalities	20	29.8
Nasal block	14	20.9
Epistaxis	17	25.4
EBV		
Yes	36	53.7
No	19	28.4
Not available	12	17.9
Histology		
Undifferentiated nonkeratinizing	61	91.0
Poorly differentiated nasopharyngeal	2	3.0
Poorly differentiated SCC	3	4.5
Papillary adenocarcinoma	1	1.5
T Stage		
T1	19	28.4
T2	22	32.8
T3	14	20.9
T4	12	17.9
N Stage		
N0	3	4.5
N1	17	25.4
N2	41	61.1
N3	6	9.0
Induction chemotherapy		
Yes	19	28.4
No	48	71.6
Concurrent chemotherapy		
Yes	64	95.5
No	3	4.5
Adjuvant chemotherapy		
Yes	33	49.3
No	34	50.7

Table 1. Patient characteristics

Abbreviations: EBV – Epstein Barr virus; SCC – squamous cell carcinoma.

In total, 43 of 67 patients (64.1%) had bilateral level II or lower neck nodal involvement whereas unilateral level II or lower neck nodes were seen in 18 of 67 patients (26.8%). Isolated retropharyngeal nodes were seen in 3 of 67 patients (4.5%) while 6 of 67 patients (8.9%) had lower neck nodal involvement (below level III). Overall, 64 of 67 patients (95.5%) received concurrent chemoradiotherapy, whereas the remaining three patients (4.5%) received radical radiotherapy alone. Of these 64 patients, 61 patients (95.3%) received at least 200 mg/m2 concurrent cisplatin or its equivalent drug, whereas three patients (4.7%) received between 100 mg/m2 and 200 mg/m2. Three of 64 patients (4.7%) completed carboplatin. In total, 12 of 67 patients (17.9%) received CCRT alone and 52 of 67 patients (77.6%) received either induction chemotherapy or adjuvant chemotherapy along with CCRT. Regarding induction chemotherapy, 19 of 67 patients (28.4%) completed chemotherapy before radiation. Of these 19 patients, 17 patients (89.5%) completed three cycles of induction chemotherapy and 2 (10.5%) received only two cycles. Additionally, adjuvant chemotherapy was administered to 33 of 67 patients (49.3%). Of these 33 patients, 14 patients (42.4%) completed three cycles of chemotherapy, 17 (51.5%) completed two cycles and 2 (6%) received only one cycle.

Treatment Outcomes

All 67 patients completed volumetric arc intensity–modulated radiotherapy and the overall median radiotherapy dose was 70 Gy [interquartile range (IQR) 66 – 76 Gy]. The overall median duration of radiotherapy was 46 days (IQR 44–49). Distribution of acute skin and mucosal adverse events during radiotherapy is shown in Fig 2. Sixteen weeks after radiotherapy, 66 of 67 patients (98.5%) had a complete response and one patient (1.5%) had a stable disease in the nasopharynx. However, this was included as a local failure event in the analysis. At the last follow–up, the median follow–up was 42.7 months (range, 3.5 – 65.0) and a total of 66 of 67 patients (96.5%)

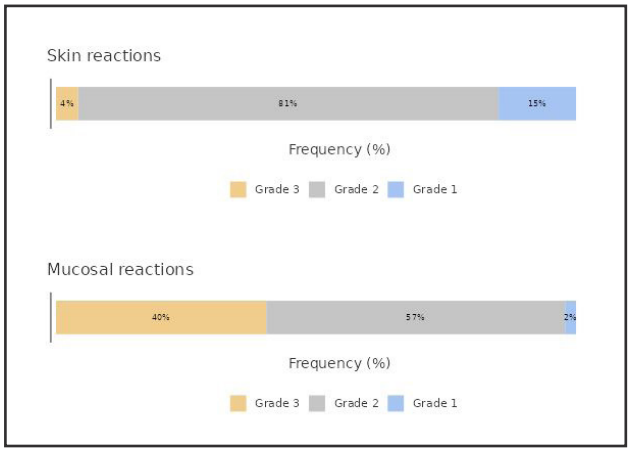


Figure 2: Grade distribution of acute skin and mucosal adverse events during radiotherapy.

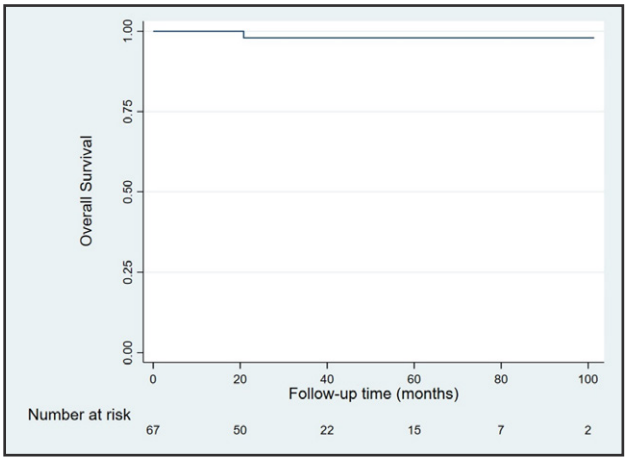


Figure 3: Overall survival (OS) for all patients who received volumetric arc therapy with or without chemotherapy (n=67). The 3–year OS was 98% (CI, 94.1 – 100%).

were alive. One patient died due to co–morbidities without disease recurrence. We recorded a total of 11 events of recurrence, distant metastasis or death in 8 of 67 patients (11.9%). Distant metastasis was seen in 6 of 67 patients (89.5%), and 3 of 67 patients (4.6%) had both locoregional failure and distant metastasis. Local control and overall survival are shown in Fig 3–5. For all patients, 3–year overall survival (OS), disease–free survival (DFS) and locoregional recurrence–free survival (LRRFS) were 98% (95% CI, 94.1 – 100%), 87.3% (95% CI, 78.6 – 97%) and 92.8% (95% CI, 86.1 – 99.9%), respectively. Regarding long term toxicities, hearing abnormalities, xerostomia, subcutaneous fibrosis, tinnitus, difficulty in mouth opening, hypothyroid, dysphagia were observed in 18 (26.8%), 23 (34.3%), 5 (7.4%), 4 (5.9%), 4 (5.9%) and 9 (13.4%) patients, respectively. In subgroup analysis, for induction chemotherapy patients, 1– and 3–year DFS were 89.5% (95% CI 76.7 – 100%) and 80.5% (95% CI, 62.2% – 100%), respectively. The 3–year LRRFS was 78% (95% CI, 77.9% – 100%). All 19 patients were alive during the follow up.

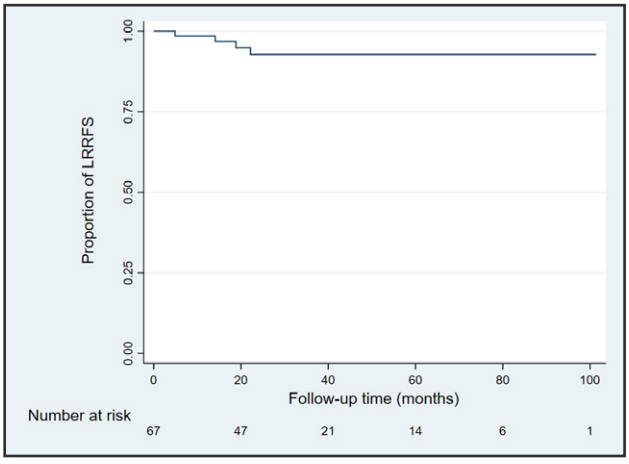


Figure 4: Locoregional recurrence–free survival (LRRFS) for all patients who received volumetric arc therapy with or without chemotherapy (n=67). The 1– and 3–year LRRFS were 98.5% (CI, 95.6 – 100%) and was 92.8% (95% CI, 86.1 – 99.9%), respectively.

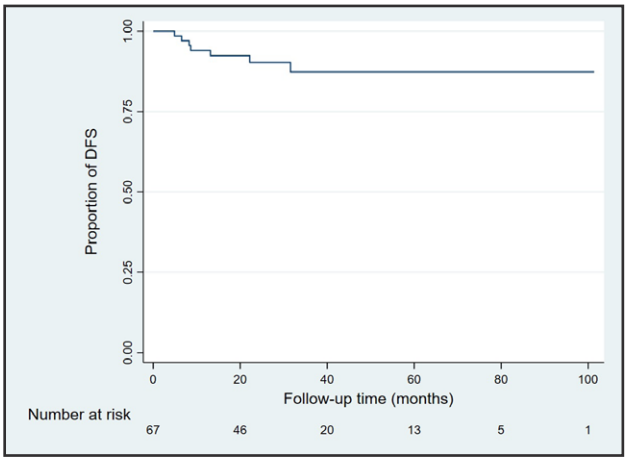


Figure 5: Disease–free survival (DFS) for all patients who received volumetric arc therapy with or without chemotherapy (n=67). The 1– and 3–year DFS were 95% (CI, 88.5 – 99.9%) and 87.3% (CI, 78.6 – 97%) respectively.

Discussion

This study focuses on the use and impact of volumetric arc therapy (VMAT), with or without chemotherapy, in newly diagnosed nasopharyngeal carcinoma (NPC) patients. It provides valuable insights into the clinical outcomes of NPC in a diverse, mixed population in the Gulf region, an area where there is limited published data. As the Gulf region has a unique demographic composition, including both local and expatriate populations, the results of this study offer important contributions to the understanding of NPC management in this context. Given the scarcity of data from this part of the world, our findings are particularly relevant, offering a distinct perspective on the efficacy and challenges of NPC treatment in this region.

Study	No of patients	Radiotherapy/CCRT	Disease control	Overall survival
M Al–Saraaf [22]	N=69	RT alone	3–year PFS: 24%	3–year OS: 47%
Phase III trial	N=78	CCRT + adjuvant chemo (cisplatin+ flurouracil)	3–year PFS: 69%	3–year OS: 78%
Cao SM [23]	N=238	CCRT	3–year DFS: 74.1%	3–year OS: 88.2%
Phase III trial	N=238	Induction chemo + CCRT1	3–year DFS: 82%	3–year OS: 88.5%
Bossi P [24] **Retrospective multicenter study**	N=1021	RT alone 7% CCRT 37% Induction/ adjuvant chemo54%	5–year DFS: 65%	5–year OS: 84%
Slevin F [25] **Retrospective multicenter study**	N=151	CCRT 86% Induction chemo 54%	5–year DFS: 65% 5–year LC: 91% 5–year regional control: 94%	5–year OS: 70%
Yildirim HC [26] **Retrospective multicenter study**	N=563	CCRT 48.9% Induction chemo 25% Adjuvant chemo 19.5%	3–year DFS: 85.6% 3–year LRRS: 92.8%	3–year OS: 90.8%
Au K H [27] **Retrospective multicenter study**	N=3328	CCRT 28.1% Induction chemo 27.5% Adjuvant chemo 13.2% RT alone 28.4	8–year PFS: 62.8% 8–year LFFS: 85.8% 8–year regional RFS: 91.5%	8–year OS: 68.5%
Xu M [28] **Retrospective single center study**	N=792	CCRT 30.7% Induction chemo 46.1% Adjuvant chemo 2.7%	5–year DFS: 69.6% 5–year LFFS: 90.8% 5–year regional RFS: 97%	5–year OS: 78%
Current study	N=67	RT alone 4.5% CCRT alone 17.9% Induction/ adjuvant chemo 77.6%	3–year DFS 87.3% 3–year LRRFS 92.8%	3–year OS 98%

Table 2: A summary of clinical outcomes reported in selected studies.

Abbreviations: RT – radiotherapy; chemo – chemotherapy; CCRT– concurrent chemoradiotherapy; OS – overall survival; PFS – progression–free survival; DFS – disease–free survival; LFFS – local failure–free survival; RFS – relapse–free survival; LRRS – locoregional relapse–free survival.

In our experience, the 3–year local control and OS were 92.8% and 98%, respectively. Our results are consistent with those of earlier studies [Table 2]. Similarly, the efficacy of induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) has been confirmed in large phase 3 randomized trials. Specifically, patients with stage III–IVB (except T3–4N0) nasopharyngeal carcinoma, aged 18–59 years were randomly assigned (1:1) to receive IC plus CCRT or CCRT alone (three cycles of 100 mg/m² cisplatin every 3 weeks, concurrently with intensity–modulated radiotherapy) in a multicenter trial. Induction chemotherapy was three cycles of intravenous TPF every 3 weeks. After a median follow–up of 71.5 months, the IC plus CCRT group showed significantly better 5–year failure–free survival (FFS) (77.4% vs. 66.4%, p = 0.019), overall survival (OS) (85.6% vs. 77.7%, p = 0.042), and locoregional failure–free survival (LRFFS) (90.7% vs. 83.8%, p = 0.044) compared to the CCRT alone group [19]. Additionally, a phase III trial compared gemcitabine and cisplatin as induction chemotherapy plus CCRT (n=242) with CCRT alone (n=238) in locoregionally advanced nasopharyngeal carcinoma. With a median

follow–up of 69.8 months, the induction chemotherapy group had a significantly higher 5–year OS (87.9% vs 78.8%, hazard ratio, 0.51 [95% CI 0.34 to 0.78]; P = .001) and a comparable risk of late toxicities (≥ grade 3, 11.3% vs 11.4%). Notably, the tumor response after induction chemotherapy correlated significantly with survival (complete response vs partial response, 5–year OS, 100% vs 88.4%, P = 0.005) [20].

Recent studies have proposed that EBV viral load could be a predictive factor for response to chemotherapy. Importantly, post hoc subgroup analyses of a study suggested that IC plus CCRT probably worked better for patient's pretreatment LDH ≥170 U/l or pretreatment EBV DNA ≥ 6000 copies/mL [19]. In addition, induction chemotherapy significantly improved their 5–year OS (85.9% v 70.8%, P = .02) for patients whose pretreatment EBV DNA was > 4,000 copies/mL in a randomized trial [20]. Similarly, Liang et al. reported that plasma EBV DNA levels at the end of IMRT served as a predictor of poor prognosis for patients with NPC. The estimated 5–year OS, FFS and distant metastasis–free survival (DMFS) rates for patients with negative and positive plasma EBV DNA were 83.1% vs. 50.3%, 81.5% vs. 49.3%, and 87.6% vs. 61.5%, respectively (P < 0.001) [21]. Due to the retrospective nature of our study, a significant number of our patients did not have EBV status, hence we were not able to analyze correlation of EBV status with clinical outcomes.

Previous studies primarily analyzed data from either endemic or non–endemic populations. However, most of our patients were expats who were from a wide ethnic and geographical background, which made our study population more heterogeneous. Our study represents one of the largest series of patients from both endemic and non–endemic areas. High–quality peer review of contours and chart review of patient's radiotherapy treatment plans were regularly conducted for this study population as per our department protocol. Hence, we did not find significant deviations from the standard practice in radiotherapy planning or delivery during the analysis.

However, one limitation of this study is the significant loss of patients to follow–up, which is a reflection of the inherently transient nature of the population in Qatar. Many individuals in the country, particularly expatriates, reside for only a few years before relocating. This dynamic population structure limits the ability to conduct robust long–term follow–up, as patients may leave before the full course of treatment and long–term outcomes can be fully assessed. This factor needs to be considered when interpreting the results, as it may impact on the generalizability of long–term efficacy and survival data.

In conclusion, to the best of our knowledge, our study is one of the largest reporting clinical outcomes of nasopharyngeal cancers treated with VMAT with or without chemotherapy. Our analysis demonstrates that the combination of VMAT and chemotherapy achieves excellent long–term tumor control, with outcomes comparable to previously published data. These findings support the continued exploration and application of induction chemotherapy and concurrent chemotherapy in the management of nasopharyngeal carcinoma. Further, large, randomized trials are needed to look on to improve the efficiency of treatment which include advanced radiotherapy techniques, radiomic and genomic analysis, and a combination of immunotherapy and radiation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not–for–profit sectors.

Ethical information

Medical Research Center in Hamad Medical corporation, Qatar granted ethical approval for this study. We confirm that all steps of scientific research were performed by relevant guidelines and regulations.

Conflict of interest:

Nil

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