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Survival outcomes for patients with nasopharyngeal carcinoma in non–endemic region in the UK treated with intensity modulated based radiotherapy 65 Gy in 30 fractions ± weekly cisplatin chemotherapy

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ABSTRACT

Background: Nasopharyngeal carcinoma (NPC) is rare in the UK. The aim of the current study was to investigate survival outcomes for patients with NPC treated with (chemo)radiotherapy using 65 Gy in 30 fractions in a non-endemic region.

Materials and methods: All consecutive 62 patients with histology proven non-metastatic nasopharyngeal carcinoma diagnosed between January 2009 to June 2019 were included in this retrospective analysis.

Results: Median age was 59 years (range:19–81). The majority of patients had stage III disease (66.1%). Induction chemotherapy was given in 21% of patients and 82.3% of patients received concomitant systemic therapy. All patients were treated with 65 Gy in 30 fractions. There was disease recurrence in 17.4% patients. The 5-year disease-free, disease-specific and overall survival were 81.9%, 79.2% and 76.4%, respectively. On univariate analysis, disease recurrence was associated with N-stage ($p = 0.047$) and overall stage group ($p = 0.023$).

Conclusion: To the best of authors' knowledge, this is the first report of the use of 65 Gy in 30 fractions of radiotherapy ± weekly cisplatin chemotherapy in NPC in a real-world setting. Our results are comparable to that from other non-endemic regions of the world using different dose fractionation of (chemo)radiotherapy. Future randomised control trials are warranted to compare various dose fractionations in these settings.

Key words: nasopharyngeal carcinoma; non-endemic; chemoradiotherapy; weekly cisplatin; 65 Gy

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Introduction

Nasopharyngeal carcinoma (NPC) is a rare cancer in many areas of the world including the UK, with only 250 cases on average diagnosed annually [1]. The most available data regarding the management of NPC patients are derived from studies conducted in endemic regions where the dis-

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ease is strongly associated with Epstein-Barr virus (EBV) infection [2]. Based on the World Health Organization, there are three pathological subtypes of nasopharyngeal carcinoma: keratinising squamous, non-keratinising, and basaloid squamous. Non-keratinising nasopharyngeal carcinoma can be divided into differentiated and undifferentiated tumours [2]. Worldwide, the most common subtype is non-keratinising NPC (up to 95% of cases in endemic areas) and is strongly associated with EBV infection [2, 3]. In non-endemic regions, many NPC cases are EBV negative, keratinising squamous or basaloid squamous cell carcinomas (SCC) and these tumours are associated with poorer survival [4, 5]. Another feature associated with worse survival is old age. Age distribution of patients with NPC in endemic areas differs from non-endemic areas, the incidence increases after the age of 30 years, peaks at 40–59 and decreases thereafter; while in non-endemic areas, the incidence of NPC has a typical bimodal peak with the first peak at a young age and the second increase after 65 years of age [6].

NPC is a relatively radiosensitive disease and radiotherapy is the mainstay of treatment. Addition of concomitant chemotherapy to radiotherapy is recommended for stage III and stage IV disease [7]. For radiotherapy, various dose regimens are used. National Comprehensive Cancer Network® (NCCN) guidelines [7] state 70–70.2Gy (1.8–2.0 Gy/fraction), daily Monday to Friday in 6–7 weeks, based on studies by Bae et al. [8] and Chen et al. [9], or 69.96 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks, based on phase III trial by Sun et al. [10]. Since the publication of Parsport trial [11], intensity modulated radiotherapy (IMRT) using 65 Gy in 30 daily fractions (2.17 Gy per fraction) Monday to Friday in 6 weeks has gained popularity in the UK, as a standard regimen to treat head and neck cancer (HNC) [12]. A UK-based phase II trial showed that induction chemotherapy followed by IMRT based 65 Gy in 30 daily fractions with concomitant 3-weekly cisplatin 100 mg/m^2 was feasible to treat NPC [13]. In general, there is a tendency in the UK to use shorter regimens of radiotherapy for increased departmental efficiency [12].

The purpose of the current study was to evaluate the survival outcomes in patients with NPC treated with (chemo)radiotherapy 65 Gy in 30 once daily fractions Monday to Friday in 6 weeks with or without addition of weekly chemotherapy or biotherapy in the North East region of England.

Materials and methods

Patient population

All histologically verified NPC patients treated at two sites of the North East of England Cancer Network (Newcastle Hospitals and Middlesbrough Hospital) between January 2009 to June 2019 were included in this retrospective analysis. 65 Gy in 30 using once daily fractionation with weekly chemotherapy was the regimen in these institutions for the study period. Eligibility criteria were; age at the time of diagnosis ≥ 18 years, histologically verified non-metastatic NPC treated with radical (chemo)radiotherapy. Patients whose disease were metastatic at presentation or treated with palliative intent were excluded.

Radiotherapy treatment

All patients had a five-point customised thermoplastic shell and a 3mm slice planning computed tomogram (CT) ± fusion with magnetic resonance imaging (MRI). A radiotherapy technique using two-dose levels was used. A gross tumour volume (GTV) was drawn on each slice while taking into account the diagnostic radiology and clinical/endoscopic information, encompassing the gross primary disease and involved lymph nodes. A 5–10 mm circumferential margin ± the entire nasopharynx was added to GTV to make it a clinical target volume (CTV), excluding the natural barriers e.g. air, bone etc. In case of an involved lymph node, CTV was extended to that whole lymph nodal level. A further 3mm margin was then applied to create a final planning target volume (PTV_65). Bilateral uninvolved cervical lymph nodal areas including the retropharynx, which was at risk of having microscopic disease, were treated with a prophylactic dose of 54 Gy. All patients were treated with Tomotherapy® or volumetric modulated arc therapy (VMAT) based IMRT. After this study period, we adopted a three-dose level approach as per updated international guidelines [21].

Chemotherapy treatment

Concomitant weekly cisplatin chemotherapy, 40 mg/m^2 with a maximum capped dose of 70 mg

for 6 weeks was the chemotherapy of choice in cisplatin eligible NPC patients for NPC ≥ stage III (AJCC TNM 7th edition). The use of induction or adjuvant chemotherapy was at the discretion of the treating clinician and this option was mainly used in patients with locally advanced bulky disease. Two or three cycles of combination therapies of cisplatin, docetaxel and 5FU were administered. In cisplatin ineligible patients, use of concomitant cetuximab was allowed (one loading dose of cetuximab 400mg/m^2 one week prior to start of radiotherapy, followed by 250mg/m^2 on a weekly basis for 6 weeks).

Response evaluation and follow-up assessments

Six weeks after completion of treatment, all patients were seen in a joint clinic with the head and neck surgical team and all patients were clinically assessed and a nasendoscopy was performed. Evalution radiology images (preferably MRI scan but if MRI was not possible, then CT scan ± PET scan) were performed 10–12 weeks post treatment. In case of incomplete or equivocal response, the case was discussed at the head and neck multidisciplinary team's meeting to decide the best course of action. Subsequent follow-up visits were scheduled on 8 to 12 weeks for the first year, three monthly for the second year and a 3 to 6 monthly for the third year and six monthly thereafter for a total period of five years. Subsequent radiology imaging was performed if there was any suspicion of recurrence.

Statistical analysis

Descriptive statistics were used to display the patients' demographics and tumour pathology. The survival outcomes of interest were defined as overall survival (OS), disease-specific survival (DSS) and disease-free survival (PFS). Estimated 5-year survival data was calculated from Kaplan-Meier survival tables with plots used for graphical representation. The 95% confidence intervals for survival were calculated as a mean ± 1.96 × standard error. The log-rank test was used to assess the association of co-variates with survival within the Kaplan-Meier analysis. The association of co-variates, as listed in Table 1, with survival outcomes was explored with univariate Cox regression.

Table 1. A summary of patient's demographics, treatment characteristics and outcomes

	N	%
Total number	62	100
Age (median with range)	59 (19–81)	
Gender		
Male	42	67.7%
Female	20	32.3%
Smoking status		
Smoker	12	19.4%
Ex- smoker	22	35.5%
Never smoked	28	45.2%
EBV status		
Positive	31	50.0%
Negative	19	30.6%
Not available	12	19.4%
WHO performance status		
0	37	59.7%
1	23	37.1%
2	2	3.2%
T Stage		
T1	14	22.6%
T2	22	35.5%
T3	14	22.6%
T4	12	19.4%
N Stage		
N1	13	21.0%
N2	30	48.4%
N3	5	8.1%
Overall stage		
I	4	6.5%
II	9	14.5%
III	41	66.1%
Iva	8	12.9%
Induction chemotherapy		
Yes	13	21.0%
No	49	79.0%
Concomitant chemotherapy		
Yes	51	82.3%
No	11	17.7%
Number of cycles of concomitant chemotherapy		
2	1	1.6%
4	4	6.5%
5	10	16.1%
6	36	56.5%
7*	1	1.6%
No concomitant chemotherapy	11	17.7%
Adjuvant chemotherapy	5	8.1%

Table 1. A summary of patient's demographics, treatment characteristics and outcomes

	N	%
Survival (n = 61)		
Disease recurrence		
Yes	10	17.4%
No	51	83.6%
Outcome		
Alive	50	82%
Dead	11	18%

EBV — Epstein-Barr virus; WHO — World Health Organization; *in case of concomitant cetuximab which included a loading dose as well

Ethical considerations

As per institutional policy, this project was approved by the local clinical governance body as a service evaluation project. The project number was 10054.

Results

The total number of patients was 62. The median age of the patient cohort was 59 years (range 19–81). Two-thirds of patients (67.7%) were male. With regard to smoking status; 45% patients were never smokers, 35% patients were ex-smokers and 19.4% patients were current smokers at the time of diagnosis. All but two patients had WHO performance status (PS) 0 or 1 at diagnosis. The remaining two patients had WHO PS 2.

Disease stage (AJCC 7th edition) is shown in Table 1. T-stage rates were as follows: T1 — 22.6%, T2 — 35.5%, T3 — 22.6% and T4 — 19.4%. Regarding N-stage, 21.0% of patients were N1, 48.4% N2 and 8.1% N3. Regarding overall staging group, 6.5% of patients were stage I, 14.5% stage II, 66.1% stage III and 12.9% of patients stage IVA. Reviewing histology, 54 patients (87%) had non-keratinising SCC, 5 patients (8%) had keratinising SCC, 1 patient had lympho-epithelial carcinoma, 1 had adenocarcinoma of papillary pattern and one with adenosquamous cell carcinoma. EBV status on the biopsy specimen was available in 50 patients and it was positive in 31 (62%) patients.

In 13 patients (21%), induction chemotherapy was given, one patient received a combination of carboplatin/5FU and the remaining 12 patients received a combination of cisplatin, docetaxel and 5FU (TPF). Concomitant weekly systemic therapy was administered in 51 patients (82.3%), all but four patients received weekly cisplatin and these remaining four patients received cetuximab concurrently. 72.6% of the patients managed to receive at least 5 cycles of concurrent weekly chemotherapy. Five patients (8%) received adjuvant cisplatin and 5-FU chemotherapy.

Response data was available in 61 patients. 51 (84%) patients had complete response (CR) radiologically. Three patients had equivocal response and they underwent examination under anaesthesia ± salvage surgery and residual disease was confirmed in only one patient. In the remaining 2 patients, there was no residual viable tumour, making it a complete clinical response in 53 patients in total (87%). Eight patients had an incomplete response but only one had successful salvage surgery.

Survival outcome data was available in 61 patients; one patient emigrated overseas and was lost to follow-up. Disease recurrence was documented in 10 patients (17.4%) (Tab. 2). Fifty patients (82%) are alive. With a median follow-up of 40.5 months, 5-year disease-free survival (DFS), 5-year disease-specific survival (DSS), 5-year overall survival (OS) were 81.9% (95% CI: 81.7–82.0, 79.2% (95% CI: 79.0–79.3, and 76.4% (95% CI: 76.2–76.5) (Fig. 1), respectively.

Univariate analysis demonstrated that disease recurrence was associated with N stage ($p = 0.047$) and overall stage group ($p = 0.023$) only. However, further analysis showed these associations were associated with higher rates of recurrence in N3 (n = 5) and stage IVa (n = 8) disease, with N0–2 and stage I–III disease demonstrating similar rates of recurrence in this population.

Discussion

NPC is relatively rare in non-endemic regions and it is valuable to have reported outcomes from these non-endemic areas. Presented in an abstract form by Bossi et al. [14], a large collaborative project from 34 European centres reviewing 1220 patients provides a useful information on patient demographics and treatment outcomes, although no information on radiotherapy dose was available in this study. The median age of this patient cohort was 50 years. 42% patients presented with stage III and 33% with stage IV. EBV status was available in 51% of patients and EBV positivity rates were 42%. Induction, concurrent and adjuvant chemotherapy were administered in 45%, 83% and 11% of

Table 2. A summary of patient details who developed disease recurrences

Serial number	Age/gender (year of diagnosis)	TNM staging	Histology	EBV status	Primary treatment details	Recurrence (PFS in months)	Further treatment	Outcome with OS (in months)
1	55 M (2009)	T4N3M0	Non-keratinising SCC	+ve	Cisplatin CRT (completed 5 cycles of cisplatin)	Local — after 17 months	BSC	DOD — 21 months
2	77 F (2011)	T2N0M0	Adenocarcinoma of papillary pattern	–ve	RT only	Local and regional — 9 months	BSC	DOD — 10 months
3	61 F (2011)	T2N2M0	Lympho-epithelial carcinoma	NA	Cisplatin CRT (completed 5 cycles of cisplatin)	Local and regional — 27 months	Palliative RT	DOD — 33 months
4	54 M (2012)	T4N3M0	Keratinising SCC	+ve	Cisplatin CRT (completed all 6 cycles of cisplatin)	Local, regional and distant metastases — 34 months later	BSC	DOD — 39 months
5	62 F (2012)	T4N2M0	Non-keratinising SCC	–ve	Cisplatin CRT (all 6 cycles of cisplatin)	Local — after 31 months	BSC	DOD — 39 months
6	53 M (2012)	T1N1M0	Non-keratinising SCC	+ve	Cisplatin CRT (all 6 cycles of cisplatin)	Local — after 87 months	Patient declined	Alive at the time of data collection
7	55 M (2013)	T2N2M0	Non-keratinising SCC	+ve	TPF (2 cycles) + cisplatin CRT (completed 4 cycles of cisplatin)	Distant metastases — 7 months later	BSC	DOD — 13 months
8	58 F (2014)	T3N2M0	Non-keratinising SCC	+ve	Cetuximab CRT (completed all 7 cycles of cetuximab)	Local — after 47 months	Salvage surgery	DOD — 65 months
9	52 M (2017)	T2N3M0	Non-keratinising SCC	+ve	TPF (3 cycles) + cisplatin CRT (all 6 cycles of cisplatin)	Distant metastases — after 2 months	Palliative RT	DOD — 26 months
10	81 F (2018)	T2N0M0	Keratinising SCC	NA	RT only	Local and regional — after 5 months	BSC	DOD — 7 months

TNM — tumor–node–metastasis; F — female; m — male; EBV — Epstein-Barr virus; +ve — positive; –ve — negative; NA — not available; SCC — squamos cell carcinoma; CRT — chemoradiotherapy; TPF — docetaxel, cisplatin and 5FU chemotherapy; RT — radiotherapy; PFS — progression free survival; BSC — best supportive care; OS — overall survival; DOD — died of disease

the patients, respectively. With a median follow-up of 56.5 months, 3- and 5-year overall survival was 83% and 77%, respectively. In 411 (33.6%) patients, there was a disease relapse, in 55% of these patients, there was distant metastasis. The most common distant metastatic sites were the bone (49%), lung (31%) and liver (29%). PS 0–1 *vs.* > 1, PS p < 0.0001, female sex (p = 0.001), stage 1 and 2 *vs.* 3 *vs.* 4, p < 0.0001), T stage (T1–T *vs.* T3–T4, p < 0.0001), and stage (N 0/1 *vs.* N2/3, p 0.0242) were prognostic factors.

A recently published study described the treatment and outcomes of NPC in British Columbia, Canada [17]. Out of a total of 601 patients included, 554 were treated with (chemo)radiotherapy. The median age of patients was 52 years and 81% histologies were non-keratinising. The 5-year DFS and OS were 62% and 70% respectively despite the fact that the percentage of patients with stage III and IV were relatively lower (55.7%) as compared to other studies described. In this study, there was not a great deal of information on radiotherapy details; patients received a range of 50–70 Gy with 77% of patients receiving 66–70 Gy in 33–35 fractions implying that the remaining 23% of patients might have received a less optimal radiotherapy dose. Similarly, the percentage of patients receiving concomitant chemotherapy was 40%

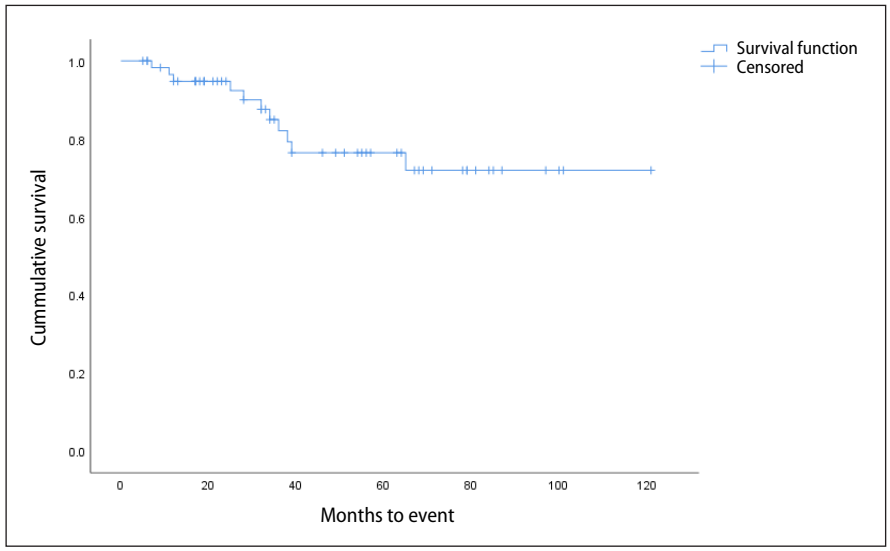

Figure 1. A Kaplan-Meier estimate of overall survival

which might be due to a lower number of patients in locally advanced stages (44% patients were with stages I and II).

A multicentre UK study involving 151 patients treated with IMRT (step-and-shoot IMRT in 117 patients and VMAT in 34 patients) giving 70 Gy in 33–35 daily fractions to patients with a median age of 52 years, 75% of patients had non-keratinising tumours. EBV status was available in 23% of patients. 74% of patients had stage III or stage IV disease. 54% of patients received induction chemotherapy and 86% received concomitant chemotherapy. Five-year DFS and OS were 65% and 70%, respectively. Keratinising SCC, older age, worse PS, smoking and alcohol intake were associated with inferior survival [4].

In a retrospective study by Demirci et al. [15], the outcomes of 248 NPC patients in a Turkish population were reported. With a median follow up of 59 months, local recurrence, regional recurrence, locoregional recurrence, distant metastases, and both locoregional recurrence and distant metastases rates were 8.9%, 0.8%, 2%, 8.5% and 3.2%, respectively. Five-year locoregional control (LRC), DFS, disease specific survival (DSS), and OS rates were 83.7%, 73%, 78.5%, and 71.1%, respectively. In multivariate analysis for LRC, cranial nerve involvement ($p = 0.009$) and tumor response ($p = 0.004$); for OS, age ($p < 0.001$), T stage ($p = 0.005$), and tumor response ($p < 0.001$) were significant prognostic factors. In our study, of the co-variates explored, only N stage and overall stage appeared related to the risk of recurrence. On further exploration of the limited data, these findings are likely to have been driven by N3 and stage IV disease.

A phase II trial, involving 42 patients evaluated the feasibility of induction chemotherapy (two cycles of cisplatin and 5FU) followed by chemoradiotherapy 65Gy in 30 daily fractions in locally advanced NPC (64% patients were at stage IV and 24% at stage III at presentation). Concomitant cisplatin chemotherapy was given at a dose of 100 mg/m^2 on a 3-weekly basis (15% of patients received concomitant carboplatin instead and 2% received cetuximab). With a median follow-up of 32 months, 2-year LRC, PFS and OS were 86.2%, 78.4% and 85.9%, respectively [13].

Belgioia et al. [16] published their experience of using Tomotherapy-based 66 Gy in 30 fractions (three target volumes, 66 Gy to GTV + 5 mm, 60 Gy to the high risk area and 54 Gy to low risk area) in 35 NPC patients. 4-year LRC and OS rates were 88.2% and 93.9%, respectively.

The survival results in our study using 65 Gy in 30 fractions with concurrent weekly chemotherapy are comparable to the outcomes published in the above-mentioned studies performed in non-endemic areas, even though some demographic features of our group of patients were relatively less favourable. In comparison with the collaborative study published by Bossi et al. [14], our patient population was much older (median age was 59 *vs.* 50 years) and had a poorer

PS (60% patients with PS 0 *vs.* 74%) but with a similar gender distribution and similar stage of disease. Stage III/IV was 75% in Bossi's cohort *vs.* 79% in our study, there was a difference in stage IV patients, which was 33% in the collaborative study in comparison with 12.9% in our study. Crude survival was virtually the same [14]. The multicentre UK study [4] revealed a slightly worse outcome in a similar population, although our patients were older (median age 59 *vs.* 52 years). The rate of use of neoadjuvant chemotherapy in our study is lower as compared to other studies [4], the possible explanation could be that our study period started from 2010 when the role of neoadjuvant chemotherapy was not well established. Another possible explanation is a relatively older population in our study.

The outcomes in the similar clinical cohort (except younger age — median 48 years *vs.* 59 years in our study) reported by Demirci et al. [15] are slightly worse. From Demirci's very detailed description, it is obvious that only 46% of patients were treated with chemotherapy in a concomitant setting, but induction chemotherapy was widely used. There is established evidence that the benefit of the addition of chemotherapy is higher when administered concomitantly [18].

As far as 3-weekly *vs.* weekly concomitant cisplatin chemotherapy is concerned, a phase II trial from the endemic region showed no difference in primary outcome of 3-year PFS. The post-treatment quality of life related to functional outcome was better with the weekly regimen [19]. In our study, four patients received concomitant cetuximab but since the publication of a review on the use of cetuximab in non-metastatic NPC where no level one evidence of its benefit was found [20], its use has been abanadoned in our centre.

In our study, there was documented local disease recurrence in eight out of a total of ten patients with disease recurrence (Tab. 2). Theoretically, this recurrence pattern raises the question of possible dose escalation which can be achieved by brachytherapy boost, simultaneously integrated boost by conventional radiotherapy or by using stereotactic body radiotherapy (SBRT). However, a recently published systematic review and meta-analysis on radiotherapy dose escalation in the primary treatment of nasopharyngeal carcinoma involving two randomised trials and seven retrospective studies showed no benefit in local recurrence-free and overall survival. In a subset analysis from the retrospective studies, dose escalation showed benefit in 5-year locoregional failure-free survival in patients who did not

Table 3. A comparative table of outcome of selected studies conducted in non-endemic area reporting 5-year survival

Characteristic	Bossi et al. [1]	Slevin et al. [5]	Demirci et al. [11]	Howlett et al. [20]	Franzese et al. [22]	Current study
Number of patients	1220	151	248	601‡	68	62
Median age	50	52	48	52	50	59
Stage III and IV	75%	74%	81.5%	55.7%	79.4%	79%
Non-keratinising histology	Not available	75%	94%	81%	84%	86%
EBV+ cases	42%	17%*	NA	NA	NA	49%
PS 0	74%	69%	NA	56%	79.4%	60%
Induction chemotherapy	45%	54%	54%	8%	73.5%	21%
Radiotherapy dose fractionation	Not available	70 Gy in 33–35 fractions	66–70 Gy in 33–35 fractions	50–70 Gy (77% received 66–70 Gy in 33–35 fractions)	70 Gy in 35 fractions or 66–69.9 Gy in 30–33 fractions	65 Gy in 30 fractions
Concurrent chemotherapy	83%	84%	46%	40%	86.8%	82.3%
Adjuvant chemotherapy	11%	–	–	1%	–	8%
5-year DFS	NA	65%	73%	62%	62.2%	81.9%
5-year OS	77%	70%	71.1%	70%	78.9%	76.4%

EBV — Epstein-Barr virus; PS — performance status; DSF — disease-free survival; OS — overall survival; NA — not available; *EBV status was available in only 23% of all patients; ‡554 patients were treated with (chemo)radiotherapy

receive concomitant chemotherapy (RR: 1.05; 95% CI: 1.02–1.09, p=0.005) [23]. In our series, two patients (serial numbers 2 and 10 in Table 2) did not receive concomitant chemotherapy and, theoretically, these patients could have benefitted from dose escalation but it is important to note that these two patients were elderly (77 and 81 years old) and one patient (case 2) had unusual histology — adenocarcinoma.

Table 3 summarises a comparison of outcomes of selected studies conducted in non-endemic area reporting 5-year survival.

There are certain limitations in our study. Firstly, the retrospective nature of the study carries a potential selection bias; however, every effort was made to minimise this bias. Secondly, EBV status was not available in 12 patients. Thirdly, treatment related toxicity data, patient reported outcomes and quality of life data were not available for this study.

Conclusion

The objective of this retrospective study was to present our experience using the treatment regimen 65 Gy in 30 fractions with concurrent chemotherapy which provides comparable survival outcomes with regimens used in other institutions. This study provides useful information on patients' demographics, disease characteristics, treatment outcomes and prognostic factors on NPC patients treated in a non-endemic region. Further clinical trials are required to assess whether this regimen results in a clinically meaningful reduction in morbidity whilst maintaining oncological efficacy.

Conflict of interest

None declared.

Funding

None declared.

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