Oral Oncology 89 (2019) 40–47

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Long-term survival and late toxicities of elderly nasopharyngeal carcinoma (NPC) patients treated by high-total- and fractionated-dose simultaneous modulated accelerated radiotherapy with or without chemotherapy

Jingjing Miao[a,1], Lin Wang[a,1], Manyi Zhu[a,1], Weiwei Xiao[b], Haijun Wu[a], Muping Di[a], Yuqing Huang[a], Shaomin Huang[b], Fei Han[b], Xiaowu Deng[b], Xiang Guo[a,*], Chong Zhao[a,*]

[a] Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou 510060, China
[b] Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou 510060, China

Introduction

According to the International Agency for Research on Cancer, nasopharyngeal carcinoma (NPC) is rare in most parts of the world, with an incidence of < 1/100,000 person-years for both males and females; however, it is a prevalent malignancy in south China, especially in the middle and west of Guangdong Province [1]. NPC is a potentially curable disease and is generally considered much more radio- and chemo-sensitive than other head and neck squamous cell carcinomas. Radiotherapy with or without chemotherapy is the standard treatment for non-disseminated NPC patients. Intensity-modulated radiotherapy (IMRT), a new technique that could escalate tumour dose while sparing the adjacent organs, has been proven to improve survival and has been widely used in NPC patients [2–4]. Another development in this field of head and neck cancer treatment is simultaneous modulated accelerated radiation therapy (SMART) [5]. This therapy facilitates the delivery of a conventional fractionated dose (1.8 Gy–2.0 Gy) to a large target volume, including the primary tumour, metastatic regional nodes and clinical target volumes, while a small volume dose boost (> 2 Gy per fraction) is delivered to the sites of gross disease [6]. This approach has been reported to increase the biologically effective dose (BED) delivered to the tumour target by elevating the total and fractionated doses and shortening the course of treatment [5,6]. In our previous phase II study, we reported that IMRT with high-total- and fractionated-dose SMART boost (the mean total dose and fractionated doses were 73.83 Gy and 2.46 Gy to the gross tumour volume of the nasopharynx and 67.72 Gy and 2.26 Gy to the metastatic neck lymph nodes, respectively) could improve local control with acceptable late toxicities by enhancing the BED of the gross tumour volume in locoregionally advanced NPC patients [2].

In endemic areas, the incidence of NPC has a unimodal age distribution with a peak from 50 to 60 years [7], although its occurrence in the elderly population (age ≥ 60.0) is not rare [8]. In addition, many concerns gradually arise in elderly NPC patients with ageing, such as declining physiologic function and increasing comorbidity rate, which can alter the pharmacokinetics of many commonly used chemotherapeutic agents, decrease sensitivity to radiotherapy and chemotherapy, and make toxicity less predictable. All of these abovementioned issues were reported to have a substantial impact on patients' mortality and complications [9–12]. Currently, although many studies have proven that the survival of NPC patients has significantly improved and that late toxicity has been markedly alleviated with IMRT and concurrent chemotherapy, especially for locoregionally intermediate and advanced-stage patients, all of these conclusions were primarily suitable for the adult population [13–15]. Studies focused on elderly NPC patients are very limited, especially those using high-total- and fractionated-dose SMART boost IMRT [16–18]. One question is whether elderly NPC patients could benefit from IMRT with high-total- and fractionated-dose SMART technology. Another question is whether adding concurrent chemotherapy could further improve the clinical outcomes of these patients. All of these issues are not yet clear.

Based on the abovementioned knowledge gaps, we conducted this retrospective study to investigate the long-term survival and late toxicities of elderly NPC patients treated by high-total- and fractionated-dose SMART boost IMRT and to analyse the effect of adding concurrent chemotherapy to radiotherapy, trying to search for the optimal treatment strategy and provide individual comprehensive therapy for elderly NPC patients.

* Corresponding authors at: Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Guangzhou 510060, China.
E-mail addresses: guoxiang@sysucc.org.cn (X. Guo), gzzhaochong@hotmail.com (C. Zhao).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.oraloncology.2018.12.008
Received 6 September 2018; Received in revised form 6 December 2018; Accepted 11 December 2018
Available online 18 December 2018
1368-8375/

Materials and methods

Patients

The study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Two hundred and fifty-four patients (age ≥ 60.0) with non-metastatic NPC who underwent IMRT at Sun Yat-sen University Cancer Center were retrospectively reviewed from June 2001 to December 2012. Patients with previous or coexisting cancers other than NPC, haematological disorders, autoimmune diseases, induction chemotherapy, adjuvant chemotherapy, palliative treatment, and uncomplete treatment data were excluded. All patients underwent pre-treatment evaluation, including a complete history and physical examination with nasopharyngoscopy, chest radiography, ultrasonography of the abdominal region, and haematologic and biochemical profiles. Additional investigations were performed if indicated. Magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) of the nasopharyngeal region and neck was performed to determine the stage. All patients of this cohort were restaged according to the UICC/AJCC staging system, 7th edition [19].

Clinical data collection

Basic clinical information of the patients, including age, gender, World Health Organization (WHO) histological type, TNM stage, treatment method, radiotherapy interruption (> 5 days), acute and late toxicities, outcomes and causes of death, were reviewed from the medical records with the patients' permission. The Charlson comorbidity index (CCI), first introduced in 1987, was chosen to represent patients' burdens including the age factor and the comorbidity [20]. It contained both advancing ages and nineteen medical conditions with a weighted score based on the relative mortality risk [20], including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes mellitus, moderate to severe chronic kidney disease, hemiplegia, leukaemia, malignant lymphoma, solid tumour, liver disease, and acquired immune deficiency syndrome. In addition, it has proven to be a reliable and valid index of survival in a large sample of patients in various oncological settings [20,21]. The acute and late toxicities were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (NCI-CTCAE v3.0) and the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria, respectively [22].

Treatments

All patients received radical high-total- and fractionated-dose SMART boost IMRT. IMRT was delivered with a dynamic multileaf intensity-modulating collimator (NOMOS Corporation, Sewickley, Pa.) using a slice-by-slice arc rotation approach. The details of the IMRT technique; delineation of the target volumes, including the gross tumour volume of the nasopharynx (GTVnx), the metastatic neck lymph nodes (GTVnd), the high-risk sites of microscopic extension (CTV1), and the low-risk sites of microscopic extension (CTV2); dose prescription of target volumes; and dose limitation of organs at risk have been previously described [2]. The prescribed dose was 68 Gy/30 fraction to GTVnx, 60–66 Gy/30 fraction to GTVnd, 60 Gy/30 fraction to CTV1, and 54 Gy/30 fraction to CTV2. Concurrent chemotherapy was administered to stage III/IVa-b patients and to some stage II patients (UICC/AJCC staging system, 6th edition) with cisplatin (80 mg/m^2/d, intravenous infusion over 2 h on days 1 and 22), mainly determined by the doctors' clinical experience and patients' preferences. A total of 158 (62.2%) patients received concurrent chemoradiotherapy (CCRT). Of these 158 patients, 30 (19.0%) patients were stage II, 83 (52.5%) patients were stage III and 45 (28.5%) were stage IVa-b (UICC/AJCC staging system, 7th edition).

Follow-up

All patients were followed up every three months during the first three years, every six months during the 4-5th years and then annually or if necessary. Each follow-up included a complete physical and electronic nasopharyngoscopy or indirect nasopharyngeal speculum examinations. Biochemical profiles, chest X-ray, ultrasound of the liver and abdomen and MRI/CT of the nasopharyngeal region and neck were also routine elements of the assessment. Further investigations were arranged when clinically indicated. All patients were followed up until Aug 31, 2017, or death from any cause.

Statistical analysis

Durations were calculated from the time of pathological diagnosis to the last follow-up date or the date of events. The CCI of the whole cohort was divided by the median. The χ^2 statistic was used for comparisons of patients' basic characteristics and outcomes. Survival curves were calculated by the Kaplan-Meier method. Differences between curves were analysed by the log-rank test. Multivariate hazard ratios (HRs) were calculated using the Cox proportional hazard model. All tests were two sided. A P value of < 0.05 and a 95% confidence interval (CI) that did not include 1 was considered to be significant. Statistical analyses were performed using the SPSS software program (IBM SPSS Statistics 22.0).

Results

Basic information and survival of elderly NPC patients

The baseline characteristics are shown in Table 1. In this study, there were 3 patients with CCI 8 scores, 10 patients with 7 scores, 45 patients with 6 scores, 86 patients with 5 scores and 110 patients with 4 scores. The median follow-up time was 61.95 months (range, 1.31–171.47 months). At the date of the last follow-up, 12 (4.7%) patients had locoregional recurrence alone, 35 (13.8%) patients had distant metastasis alone and 3 (1.2%) had both locoregional recurrence and distant metastasis. A total of 76 (29.9%) patients died, including 7 (9.2%) patients who died of local recurrence, 35 (46.1%) patients who died of distant metastasis, 2 (2.6%) patients who died of nasopharyngeal necrosis and bleeding after re-radiotherapy, 31 (40.8%) patients who died of non-NPC-related causes (including 2 for colon cancer, 1 for lung cancer, 6 for diabetes, 5 for cerebrovascular disease, 4 for chronic obstructive pulmonary disease, 4 for kidney failure, 3 for liver disease, 3 for heart failure and 3 for natural death) and 1 (1.3%) patient who died of an unknown cause. The 5-year locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), disease-specific survival (DSS) and overall survival (OS) of the whole cohort were 93.0%, 85.3%, 83.2% and 74.1%, respectively.

Dose statistics for tumour volumes

The mean volume of GTVnx was 33.32 cm^3, ranging from 1.62 to 161.68 cm^3. The mean total and fractionated doses for GTVnx, GTVnd (left and right), CTV1, and CTV2 were 74.55 Gy and 2.49 Gy, 68.83 Gy and 2.29 Gy (left), 69.10 Gy and 2.30 Gy (right), 69.83 Gy and 2.33 Gy, and 62.76 Gy and 2.09 Gy, respectively. The average maximum dose, minimum dose, mean dose, and percentage target volume covered by the 100% prescribed dose line of GTVs and CTVs are listed in Table 2.

Table 1
Basic information in these 254 elderly NPC patients.

Variable	N (%)
Age, year	63 (60–79)
Gender	
male	194 (76.4%)
female	60 (23.6%)
WHO category	
II	14 (5.5%)
III	240 (94.5%)
CCI category	
CCI < 5	110 (43.3%)
CCI ≥ 5	144 (56.7%)
T classification[a]	
T1	26 (10.2%)
T2	60 (23.6%)
T3	120 (47.2%)
T4	48 (18.9%)
N classification[a]	
N0	72 (28.3%)
N1	130 (51.2%)
N2	42 (16.5%)
N3	10 (3.9%)
TNM stage[a]	
I	7 (2.8%)
II	65 (25.6%)
III	125 (49.2%)
IVa-b	57 (22.4%)
Treatment methods	
RT alone	96 (37.8%)
CCRT	158 (62.2%)

Abbreviation: RT alone, Radiotherapy alone; CCRT, concurrent chemoradiotherapy; CCI, Charlson comorbidity index.
[a] According to American Joint Committee on Cancer, 7th edition.

Acute and late toxicities

Acute toxicities were assessed in all patients. Fifty patients had interrupted radiotherapy due to grade 3 mucositis and grade 4 haematologic toxicities. The mean time of radiotherapy interruption was 7 days (5–18 days). The most common acute toxicities among these 254 patients were grade 1–2 xerostomia, mucositis, dermatitis and gastrointestinal toxicities. No patient had grade 4 acute toxicities except for haematologic toxicities. Only 9 patients had grade 4 leukopenia, 9 patients had grade 4 neutropenia, and 5 patients had grade 4 thrombocytopenia (Table 3).

Late toxicities were assessed in 175 patients with ≥4 years of follow-up. The results are depicted in Table 3. The most common late toxicities were grade 1–2 subcutaneous fibrosis, hearing loss, xerostomia, and skin dystrophy. Only 7 patients had grade 3 subcutaneous fibrosis, and 3 patients had grade 3 skin dystrophy. No patient had grade 4 late toxicity. There were 21 patients who had temporal lobe injury, including 19 patients without symptoms and 2 patients with mild symptoms. In addition, 12 patients had grade 1 cranial nerve injury such as dysphagia, choking, hoarseness, and glossal amyotrophy. Only two patients sustained brainstem injury, and no patient had spinal cord injury.

The influence of concurrent chemotherapy in locoregionally intermediate and advanced-stage elderly NPC patients

To identify the efficacy of concurrent chemotherapy in elderly NPC patients at locoregionally intermediate and advanced stages, patients with stage II-IVb disease were selected. There were 89 patients in the RT-alone group and 158 patients in the CCRT group, and the 5-year LRRFS, DMFS, DSS and OS of the RT-alone group vs. the CCRT group were 94.0% vs. 92.2% ($P = 0.463$), 83.5% vs. 86.2% ($P = 0.278$), 81.8% vs. 83.1% ($P = 0.384$) and 74.0% vs. 72.8% ($P = 0.542$). The basic information and corresponding survival curves are shown in Table 4 and Fig. 1.

Univariate and multivariate analyses of elderly NPC patients

Univariate and multivariate analyses were performed and included the following factors: age, gender (male vs. female), WHO category (II vs. III), T stage, N stage, CCI category (< 5 vs. ≥5), treatment method (CCRT vs. RT alone) and treatment interruption (< 5 days vs. ≥5 days). Only the CCI category was significant in predicting LRRFS ($P = 0.007$), and the T stage and N stage were significant in predicting DMFS (T stage: $P = 0.036$; N stage: $P = 0.005$), DSS (T stage: $P = 0.021$; N stage: $P = 0.009$) and OS (T stage: $P = 0.001$; N stage: $P = 0.001$), as shown in Table 5. In addition, the treatment methods were not significant in predicting all four endpoints.

Discussion

In this study, we analysed the long-term survival and late toxicities of elderly NPC patients treated by high-total- and fractionated-dose SMART boost IMRT and identified the effect of concurrent chemotherapy on elderly patients with locoregionally intermediate and advanced disease. The results showed that enhanced total and fractionated irradiation doses to tumour volumes could obtain better locoregional control and long-term outcomes with mild acute and late toxicities and that elderly NPC patients with locoregionally intermediate and advanced disease may not benefit from concurrent chemotherapy.

With the ageing population and the increasing number of elderly NPC patients, more attention has been paid to improving their therapeutic efficacy and life quality. A retrospective analysis of 13,407 NPC patients in Taiwan [11] found that older patients were associated with a higher mortality rate, and the risk of mortality in patients aged > 60.0 years was 3.61-fold greater than that of those aged ≤40 years. A retrospective analysis of NPC patients aged > 65.0 years by Zhang Y et al. reported that elderly NPC patients presented more

Table 2
Dose-volume histogram statistics of tumor volumes.

	D_{min} (Gy) (average)	D_{max} (Gy) (average)	D_{mean} (Gy) (average)	D_{mean} per Fraction (Gy) (average)	V_{100} (%) (average)
GTVnx	64.09 ± 5.24	80.19 ± 2.86	74.55 ± 2.50	2.49 ± 0.08	97.63 ± 4.13
GTVndl	63.22 ± 2.63	73.46 ± 3.97	68.83 ± 2.60	2.29 ± 0.09	99.19 ± 2.12
GTVndr	62.48 ± 2.53	74.70 ± 3.41	69.10 ± 2.42	2.30 ± 0.08	99.72 ± 0.61
CTV1	54.20 ± 5.92	79.39 ± 2.89	69.83 ± 2.61	2.33 ± 0.09	98.99 ± 1.43
CTV2	39.23 ± 5.65	77.61 ± 2.87	62.76 ± 1.88	2.09 ± 0.06	97.24 ± 2.71

Abbreviation: D_{min}, minimum dose; D_{max}, maximum dose; D_{mean}, mean dose; V_{100}, the percentage of the target volume covered by the 100% prescribed dose line; Gy, grays; GTVnx, gross tumor volume of nasopharynx; GTVndl, gross tumor volume of left neck nodes; GTVndr, gross tumor volume of right neck nodes; CTV, clinical target volume.

Table 3
Acute and Late toxicities assessments.

Type	Grade 0 No. (%)	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Acute Toxicity[*]					
Mucositis	0 (0)	52 (20.4)	103 (40.6)	99 (39.0)	0 (0)
Xerostomia	9 (3.5)	118 (46.5)	127 (50.0)	0 (0)	0 (0)
Dermatitis	0 (0)	160 (63.0)	85 (33.5)	9 (3.5)	0 (0)
Gastrointestinal toxicity	117 (46.1)	108 (42.5)	24 (9.4)	5 (2.0)	0 (0)
Leukopenia	146 (57.5)	38 (15.0)	47 (18.5)	14 (5.5)	9 (3.5)
Neutropenia	170 (66.9)	14 (5.5)	47 (18.5)	14 (5.5)	9 (3.5)
Anemia	198 (78.0)	28 (11.0)	24 (9.4)	4 (1.6)	0 (0)
Thrombocytopenia	226 (89.0)	14 (5.5)	0 (0)	9 (3.5)	5 (2.0)
Hepatic impairment	240 (94.5)	9 (3.5)	5 (2.0)	0 (0)	0 (0)
Renal impairment	254 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
Heart impairment	254 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)
Late Toxicity[#]					
Subcutaneous fibrosis	24 (13.7)	92 (52.6)	52 (29.7)	7 (4.0)	0 (0)
Hearing loss	41 (23.4)	87 (49.7)	47 (26.9)	0 (0)	0 (0)
Xerostomia	77 (44.0)	81 (46.3)	17 (9.7)	0 (0)	0 (0)
Skin dystrophy	105 (60.0)	56 (32.0)	11 (6.3)	3 (1.7)	0 (0)
Temporal lobe injury	154 (88.0)	19 (10.9)	2 (1.1)	0 (0)	0 (0)
Cranial nerve injury	163 (93.1)	12 (6.9)	0 (0)	0 (0)	0 (0)
Brainstem injury	173 (98.9)	2 (1.1)	0 (0)	0 (0)	0 (0)
Spinal cord injury	175 (1 0 0)	0 (0)	0 (0)	0 (0)	0(0)

[*] For all patients (n = 254).
[#] For patients with ≥4 years follow-up (n = 175).

Table 4
Basic information in II-IVb stage elderly patients.

Characteristics	RT alone	CCRT	P
	(n = 89)	(n = 158)	
Age, year			
< 70	64	148	
≥70	25	10	< 0.001
Gender			
male	68	121	
female	21	37	0.975
WHO category			
II	9	5	
III	80	153	0.023
CCI category			
< 5	25	82	
≥5	64	76	< 0.001
T stage[a]			
T1 + T2	38	41	
T3 + T4	51	117	0.007
N stage[a]			
N0 + N1	73	122	
N2 + N3	16	36	0.374
TNM stage[a]			
II	35	30	
III	42	83	
IVa-b	12	45	0.001
Treatment interruption, > 5d			
No	66	131	
Yes	23	27	0.100

Abbreviation: RT alone, Radiotherapy alone; CCRT, Concurrent chemoradiotherapy, CCI, Charlson comorbidity index.
[a] According to American Joint Committee on Cancer, 7th edition.

nasopharyngeal symptoms, which might inherently confer poor outcomes [23]. Notwithstanding the burden of tumour itself, the functional status of the elderly gradually declines and the rate of comorbidities increases with age [24–26], especially among elderly oncology patients [27]. Therefore, most clinical trials to evaluate the effectiveness of different treatments exclude elderly NPC patients, and there are rare studies concerning their dosimetry analysis and toxicities, especially with high-total- and fractionated-dose SMART boost IMRT [16–18,23,28].

Just as IMRT could provide much highly conformal dose distribution, better volume coverage and dose homogeneity than conventional radiotherapy, which improves patient's local control. And beyond that, increasing the total irradiation dose can improve the local control of NPC further, and escalating the fractional dose can help to overcome the radiation resistance of insensitive tumour cells [29,30]. In the current study, we analysed the elderly NPC patients' dosimetry with the use of high-total- and fractionated-dose SMART boost IMRT. On average, a mean GTVnx dose of 74.55 Gy was given over 6–7 weeks, similar to our previous stage II study (adult NPC patients mainly) [2], which also showed a 3.5–6.5% increase compared with 2D-CRT or 3D-CRT [23,28,31–34] and a 3.5–10.0% increase compared with IMRT [35–37], as shown in Table 6. With a median follow-up of more than 5 years, a preferable clinical efficacy with acceptable late toxicities was confirmed for the escalation of the total and fractionated dose of GTVnx by SMART boost technology. The 5-year LRRFS, DMFS, OS and DSS were 93.0%, 85.7%, 74.1% and 83.2%, respectively. Compared with the results of the elderly NPC patients treated with 2D-CRT or 3D-CRT (Table 6), the locoregional control and long-term survival greatly improved, with a 5–40% increase in LRRFS and a 15–35% increase in OS [21,28,31–34]. Even compared with another study concerning elderly patients treated with 2.10–2.18 Gy fraction dose IMRT [38], the long-term locoregional control (5 years) of our study was similar to their short-term locoregional control (3 years). Furthermore, we also found that the elderly NPC patients' locoregional control, distant metastasis and long-term survival rates were similar to those of the primarily adult NPC patient studies using IMRT [2–4].

No patients in this study discontinued their treatment as a result of severe acute toxicities. However, fifty patients interrupted radiotherapy due to grade 3 mucositis and grade 4 haematologic toxicities. There were fewer grade 3–4 acute toxicities than in previous studies on the use of conventional radiotherapy, especially regarding mucositis and dermatitis [28,32–34]. The most common late toxicities were of grades 1–2 among 175 patients over ≥4 years of follow-up. Only 10 patients had grade 3 toxicity, including 7 patients with subcutaneous fibrosis and 3 patients with skin dystrophy. No patient had grade 4 toxicity. These results were much better than those of elderly patients treated with conventional radiotherapy [31–34] and similar to those of our

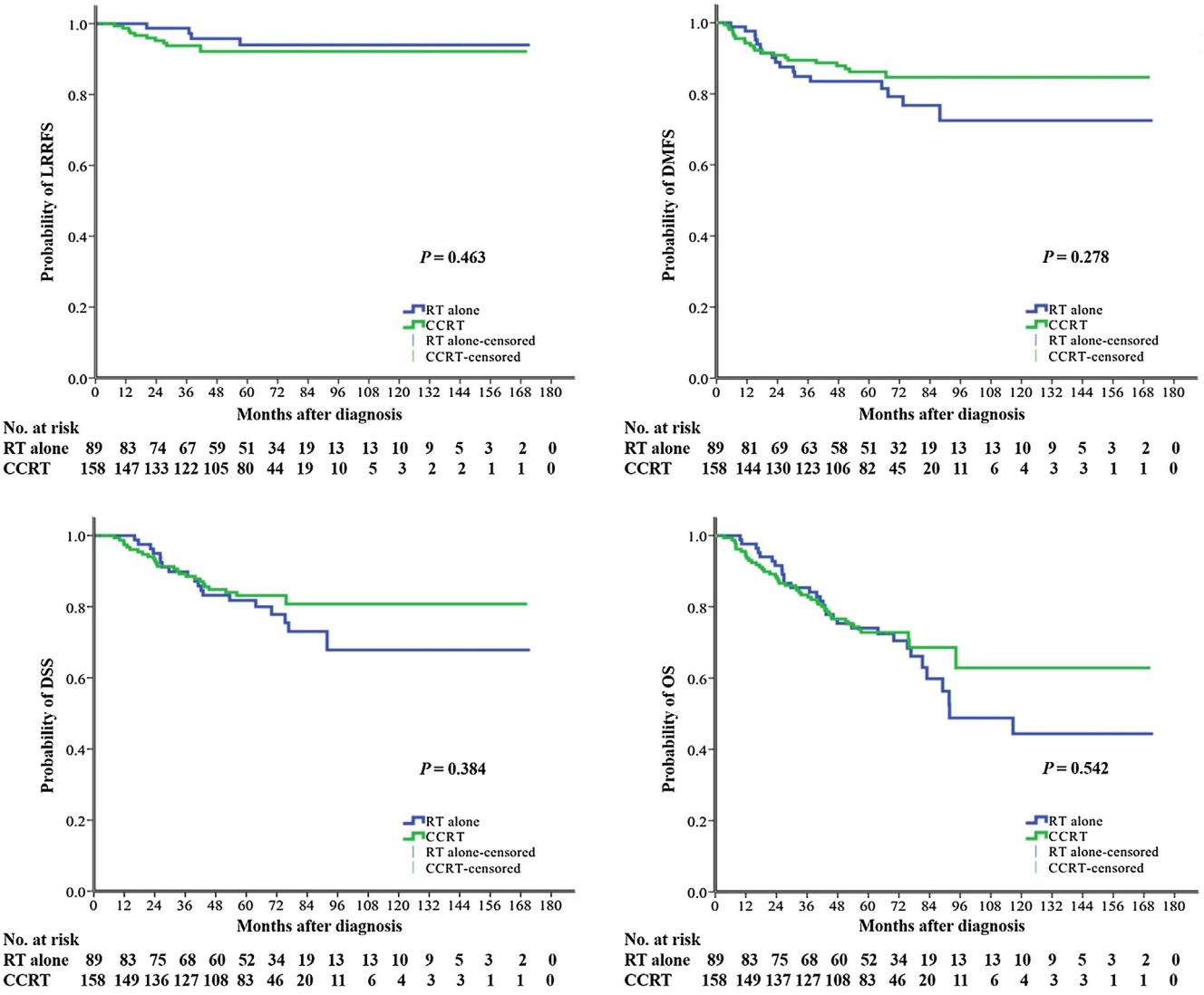

Fig. 1. Kaplan-Meier estimates of loco-regional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), disease specific survival (DSS) and overall survival (OS) of the II–IVb stage elderly NPC patients.

previous study of patients treated by high-dose IMRT [2]. Both the acute and late toxicity decreases suggest that the use of high-total- and fractionated-dose SMART boost IMRT could not only escalate the dose delivered to tumours to achieve better local control but also restrict the dose delivered to the normal tissue around the tumour to achieve better normal tissue protection.

Due to the unobvious tumour site and ignored symptoms [23], most patients have already reached a locoregionally intermediate or advanced stage (stage II–IVb, 7th AJCC/UICC) when diagnosed with NPC. Based on the latest National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (version II.2017), CCRT is recommended for the treatment of stage II–IVb NPC patients. For elderly NPC patients, however, issues of whether adding chemotherapy could improve their treatment outcome and of determining the choice of treatment methods have remained quite controversial. Previous studies have shown that standard chemoradiotherapy could achieve reasonable local and regional control in elderly NPC patients in the era of 2D-CRT, with acceptable and reversible acute toxicity, although distant metastasis remained the dominant failure pattern [17,28,32]. In the current study, we also chose stage II–IVb patients for the analysis of their prognoses with RT alone versus CCRT. No significant differences were found between the RT-alone group and the CCRT group in the elderly patients, and multivariate analyses also showed that the treatment method (CCRT vs. RT alone) was not a significant predictor for survival. The reason for this finding may be that most of the elderly NPC patients already had poor physiologic function and low compensative capacity. When they received chemotherapy, the benefits of chemotherapy might be counteracted by its substantial impact on their normal function with numerous adverse effects [3,10–12]. Patients' baseline health and function should be considered when considering chemotherapy, and the comparative risks and benefits should be discussed carefully [39]. If we could find some kind of new method that could improve survival with the least amount of damage possible, it would certainly appear worthy of further investigation; moreover, the recipients of such treatment should also be monitored closely during treatment for toxicity and poor tolerance.

In multivariate analyses, we found that the CCI category was the only significant factor in predicting LRRFS, i.e., patients with a CCI ≥ 5 tended to have better 5-year LRRFS rates than patients with a CCI < 5. The reason might be that more patients in the CCI < 5 group received CCRT, which may lead to a high treatment interruption rate, which then affects the locoregional control [39]. With regard to DMFS, OS and DSS, both T stage and N stage were independent prognostic indexes, similar to previous studies [40].

This study had several limitations. First, the CCI only has nineteen conditions and does not include non-malignant haematologic diseases,

Table 5
Univariate and Multivariate analyses of the elderly NPC patients.

variable	5-yr LRRFS				5-yr DMFS				5-yr DSS				5-yr OS			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)
Age	0.329				0.723				0.552				0.231			
Gender	0.814				0.970				0.840				0.936			
WHO category	0.511				0.360				0.248				0.128			
T stage[a]	0.180				0.025	1.569 (1.058–2.329)	0.036	1.538 (1.029–2.298)	0.013	1.589 (1.102–2.290)	0.021	1.552 (1.069–2.252)	0.001	1.612 (1.226–2.119)	0.001	1.571 (1.192–2.071)
N stage[a]	0.866				0.003	1.829 (1.226–2.729)	0.005	1.794 (1.196–2.689)	0.001	1.897 (1.308–2.752)	0.009	1.854 (1.273–2.699)	< 0.001	1.674 (1.254–2.234)	0.001	1.622 (1.211–2.173)
CCI category	0.007	0.176 (0.050–0.624)	0.007	0.176 (0.050–0.624)	0.196				0.077				0.203			
Treatment methods	0.376				0.434				0.592				0.787			
Treatment interruption	0.987				0.976				0.712				0.471			

Abbreviations: LRRFS, loco-regional recurrence free survival; DMFS, distant metastasis free survival; DSS, disease specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; CCI, Charlson comorbidity index.

[a] According to American Joint Committee on Cancer, 7th edition.

Table 6
Summary of other Studies Concerning of the Elderly Nasopharyngeal Carcinoma Patients.

Authors	Age, yr	Stage	Treatment (N)	RT technology	Fractionation Scheme for GTV of Nasopharynx			Survival		
					Fraction	Actual dose, Gy	Fraction dose, Gy	5-yr LRRFS	5-yr DMFS	5-yr OS
Teo PM et al., 2012[30]	≥70	I-IVb(5th TNM stage)	RT ± Chemo (n = 103)	70.9%3D-CRT 29.1%IMRT	33–35	/	2.00–2.12	/	/	43.9%
Zhang Y et al., 2015[23]	≥65	I-IVb(6th TNM stage)	RT ± Chemo (n = 212)	84.4%2D-CRT 15.6%IMRT	30–33	72.00	/	LRFS 68.8% RRFS 78.7%	79.4%	47.0%
Liu H et al., 2013[32]	≥65	III-IVb(7th TNM stage)	RT alone (n = 101) CRT (n = 101)	92.6%2D-CRT 7.4%3D-CRT/IMRT	/	70.00	2.00(2D-CRT) 2.12–2.19(IMRT)	52.2% 78.4%	63.6% 69.6%	39.3% 54.6%
Zeng Q et al., 2015[28]	≥60	III-IVb(1992 China stage)	RT alone (n = 87) CRT (n = 87)	100.0%2D-CRT	/	/	/	72.0% 88.0%	73.0% 75.0%	40.0% 62.0%
Zeng Q et al., 2016[33]	≥60	II-IVb(1992 China stage)	RT ± Chemo (n = 132)	100.0%2D-CRT		71.00	/	88.7%	83.0%	58.3%
Wang C et al., 2017[34]	≥60	III-IVb(6th TNM stage)	IC + CCRT (n = 82) CCRT (n = 82)	100.0%3D-CRT	/	70.00 70.18	2.00–2.27	80.4% 77.2%	80.0% 76.9%	71.8% 60.5%
Huang Y et al., 2018[21][b]	≥65	I-IVb(6/7th TNM stage)	RT ± Chemo (n = 1137)	59.3%IMRT 28.9%Photon 11.8%3D-CRT/other	/	/	/	/	/	50.3%
Wang F et al., 2018[38]	≥60	II-IVb(7th TNM stage)	RT + Chemo + h-R3 (n = 75)	94.7%IMRT 5.3%2D-CRT	30/33	/	2.10–2.18	3-yr LRFS 95.6% 3-yr RRFS 95.5%	3-yr 98.6%	3-yr 89.2%
Xiao WW et al., 2010[2]	42(15–73)	III-IVb(6th TNM stage)	CCRT (n = 81)	100.0%IMRT	30	73.83	2.46	94.9%	/	74.5%
Current study	≥60	I-IVb(7th TNM stage)	RT ± Chemo (n = 254)	100.0%IMRT	30	74.55	2.49	93.0%	85.7%	74.1%

[b] National Cancer Data Base analysis.

such as anaemia. Second, our patients were restricted to one local hospital, and this study was only retrospective. Therefore, a large, prospective multicentre study will be important to validate our findings. Third, only basic data were included for prognostic analysis, without haematological indexes or biochemical indexes, which may affect the conclusions.

In conclusion, this study demonstrated that high-total- and fractionated-dose SMART boost IMRT is feasible and safe for treating elderly NPC patients, with satisfactory long-term survival and acceptable toxicities. In addition, the role of CCRT needs to be further studied in elderly NPC patients. More studies are needed to optimize the treatment strategy and improve the overall survival of these patients.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Availability of data and material

The original data of this study has been uploaded to the Research Data Deposit public platform (www.researchdata.org.cn), with approval RDD number as RDDA2018000732.

Funding

This work was supported by the Science and Technology Project of Guangdong Province [grant number 2014A020212433]; and Wu Jieping Medical Foundation [grant number 320.6750.17108].

Author Contributions

Jingjing Miao: Study design, data acquisition, Quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript preparation, manuscript editing and manuscript review.

Lin Wang: Data acquisition, quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript preparation and manuscript editing.

Manyi Zhu: Data acquisition, quality control of data and algorithms, data analysis and interpretation, statistical analysis, manuscript preparation and manuscript editing.

Weiwei Xiao: Data acquisition, quality control of data and algorithms, data analysis and interpretation, statistical analysis and manuscript preparation.

Haijun Wu: Data acquisition, quality control of data and algorithms, data analysis and interpretation and manuscript preparation.

Muping Di: Data acquisition, quality control of data and algorithms and manuscript preparation.

Yuqing Huang: Data acquisition and manuscript preparation.

Shaomin Huang: Data acquisition and manuscript review.

Fei Han: Data acquisition and manuscript review.

Xiaowu Deng: Manuscript review

Xiang Guo: Study design and manuscript review.

Chong Zhao: Study concepts, study design and manuscript review.

Conflict of interest

All authors declare that he/she has no conflict of interest.

Acknowledgements

The authors thank the patients and their families for their participation in this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2018.12.008.

References

[1] Wei KR, Zheng RS, Zhang SW, et al. Nasopharyngeal carcinoma incidence and mortality in China, 2013. Chin J Cancer 2017;36:90.
[2] Xiao WW, Huang SM, Han F, et al. Local control, survival, and late toxicities of locally advanced nasopharyngeal carcinoma treated by simultaneous modulated accelerated radiotherapy combined with cisplatin concurrent chemotherapy: long-term results of a phase 2 study. Cancer 2011;117(9):1874–83.
[3] Lee AW, Ng WT, Chan LL, et al. Evolution of treatment for nasopharyngeal cancer – success and setback in the intensity-modulated radiotherapy era. Radiother Oncol 2014;110:337–84.
[4] Miao JJ, Xiao WW, Wang L, et al. The value of the prognostic nutritional index (PNI) in predicting outcomes and guiding the treatment strategy of nasopharyngeal carcinoma (NPC) patients receiving intensity-modulated radiotherapy (IMRT) with or without chemotherapy. J Cancer Res Clin Oncol 2017;143(7):1263–73.
[5] Butler EB, Teh BS, Grant 3rd WH, Uhl BM, Kuppersmith RB, Chiu JK, et al. Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 1999;45:21–32.
[6] Teh BS, Woo SY, Butler EB. Intensity modulated radiation therapy (IMRT): a new promising technology in radiation oncology. Oncologist 1999;4:433–42.
[7] Berry MP, Smith CR, Brown TC, et al. Nasopharyngeal carcinoma in the young. Int J Radiat Oncol Biol Phys 1980;6(4):415–21.
[8] Bray F, Haugen M, Moger TA, et al. Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-risk populations and aetiologic implications. Cancer Epidemiol Biomarkers Prev 2008;17:2356–65.
[9] Hoppe S, Rainfray M, Fonck M, et al. Functional decline in older patients with cancer receiving first-line chemotherapy. J Clin Oncol 2013;31:3877–82.
[10] Balducci L, Corcoran MB. Antineoplastic chemotherapy of the older cancer patient. Hematol Oncol Clin North Am 2000;14:193–212.
[11] Huang WY, Lin CL, Lin CY, et al. Survival outcome of patients with nasopharyngeal carcinoma: a nationwide analysis of 13 407 patients in Taiwan. Clin Otolaryngol 2015;40(4):327–34.
[12] Piccirillo JF, Tierney RM, Costas I, et al. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 2004;291:2441–7.
[13] Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys 2006;64(1):47–56.
[14] Chan ATC, Gregoire V, Lefebvre J-L, et al. Nasopharyngeal cancer: EHNS–ESMO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl.7):vii83–5.
[15] Langendijk JA, Leemans CR, Buter J, et al. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. J Clin Oncol 2004;22(22):4604–12.
[16] Qi SN, Xie FY, Lu TX, et al. Clinical characters of aged naopharyngeal carcinoma patients. Ai Zheng 2006;25:740–3.
[17] Zeng Q, Guo X, Li NW, et al. Clinical characteristics and prognosis of aged nasopharyngeal carcinoma patients: a report of 313 cases. Ai Zheng 2008;27:289–94.
[18] Unger JM, Coltman CJ, Crowley JJ, et al. Impact of the year 2000 medicare policy change on older patient enrollment to cancer clinical trials. J Clin Oncol 2006;24:141–4.
[19] Edge SB, Byrd DR, Compton CC, et al. American Joint Committee on Cancer manual for staging of cancer. 7th ed. Philadelphia: JB Lippincott; 2009.
[20] Charlson M, Pompei P, Ales K. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373–83.
[21] Huang Y, Chen W, Haque W, et al. The impact of comorbidity on overall survival in elderly nasopharyngeal carcinoma patients: a national cancer data base analysis. Cancer Med 2018. https://doi.org/10.1002/cam4.1377.
[22] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;13:1341–6.
[23] Zhang Y, Yi JL, Huang XD, et al. Inherently poor survival of elderly patients with nasopharyngeal carcinoma. Head Neck 2015;37(6):771–6.
[24] Heart disease and stroke statistics—2003 update. American Heart Association Website 2003. Available at: http://www.americanheart.org/downloadable/heart/1059017971148 2003HDSStatsBookREV7-03.pdf. Accessed July 2003.
[25] Chang AM, Halter JB. Aging and insulin secretion. Am J Physiol Endocrinol Metab 2003;284:E7–12.
[26] Staessen JA, Wang J, Bianchi G, et al. Essential hypertension. Lancet 2003;361(9369):1629–41.
[27] Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. Cancer 1997;80:1273–83.
[28] Zeng Q, Xiang YQ, Wu PH, et al. A matched cohort study of standard chemo-radiotherapy versus radiotherapy alone in elderly nasopharyngeal carcinoma patients. PLoS One 2015;10(3):e0119593. https://doi.org/10.1371/journal.pone.0119593.
[29] Le QT, Tate D, Koong A, et al. Improved local control with stereotactic radiosurgical boost in patients with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2003;56(4):1046–54.

[30] Teo PM, Leung SF, Tung SY, et al. Dose-response relationship of nasopharyngeal carcinoma above conventional tumoricidal level: a study by the Hong Kong nasopharyngeal carcinoma study group (HKNPCSG). Radiother Oncol 2006;79(1):27–33.
[31] Sze HC, Ng WT, Chan OS, et al. Radical radiotherapy for nasopharyngeal carcinoma in elderly patients: the importance of co-morbidity assessment. Oral Oncol 2012;48(2):162–7.
[32] Liu H, Chen QY, Guo L, et al. Feasibility and efficacy of chemoradiotherapy for elderly patients with locoregionally advanced nasopharyngeal carcinoma: results from a matched cohort analysis. Radiat Oncol 2013;8:70.
[33] Zeng Q, Wang J, Lv X, et al. Induction chemotherapy followed by radiotherapy versus concurrent chemoradiotherapy in elderly patients with nasopharyngeal carcinoma: finding from a propensity-matched analysis. BMC Cancer 2016;16:693.
[34] Wang C, Tang X, Wang J, et al. Induction chemotherapy plus concurrent chemoradiotherapy vs concurrent chemoradiotherapy in elderly patients with advanced nasopharyngeal carcinoma. Otolaryngol Head Neck Surg 2017;157(2):233–8.
[35] Lee SW, Back GM, Yi BY, et al. Preliminary results of a phase I/II study of simultaneous modulated accelerated radiotherapy for nondisseminated nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2006;65(1):152–60.
[36] Koom WS, Kim TH, Shin KH, et al. SMART (simultaneous modulated accelerated radiotherapy) for locally advanced nasopharyngeal carcinomas. Head Neck 2008;30(2):159–69.
[37] Kam MK, Teo PM, Chau RM, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. Int J Radiat Oncol Biol Phys 2004;60(5):1440–50.
[38] Wang F, Jiang C, Ye Z, et al. Efficacy and safety of nimotuzumab plus radiotherapy with or without cisplatin-based chemotherapy in an elderly patient subgroup (aged 60 and older) with nasopharyngeal carcinoma. Transl Oncol 2018;11(2):338–45.
[39] VanderWalde NA, Meyer AM, Deal AM, et al. Effectiveness of chemoradiation for head and neck cancer in an older patient population. Int J Radiat Oncol Biol Phys 2014;89(1):30–7.
[40] Wang W, Feng M, Fan Z, et al. Clinical outcomes and prognostic factors of 695 nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. BioMed Res Int 2014 2014:814948.