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Original Article

A cross sectional study in cognitive and neurobehavioral impairment in long-term nasopharyngeal cancer survivors treated with intensity-modulated radiotherapy

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ABSTRACT

Purpose/objectives: To determine neurocognitive and neurobehavioral impairment in long-term nasopharyngeal cancer survivors (NPC) treated with intensity-modulated radiotherapy (IMRT).
Materials/methods: A cross-sectional cohort of NPC ≥4 years (y) following IMRT was assessed. Objective cognitive function was measured using the Montreal Cognitive Assessment (MoCA) and patient-reported memory was assessed with the MDASI-HN problems remembering item. Patient and family ratings of patients' neurobehavioral symptoms of apathy, disinhibition and executive dysfunction were assessed with the Frontal Systems Behavior Scale (FrSBe). Other patient-reported symptoms (MDASI-HN), mood (HADS), and quality of life (FACT-H&N) were also collected.
Results: Among 102 participants: M:F = 66:36; median age 56y (32–77); median time since IMRT 7.5y (4.2–11.1). Impaired MoCA scores (<23) were observed in 33 (32%). Patient and family ratings of pre-illness neurobehavioral symptoms were in the normal range (total FrSBe T-scores 53.3 and 59.0 respectively). In contrast, post-treatment patient and family T-scores were clinically impaired (64.7, 71.3 respectively), with apathy, disinhibition and executive dysfunction post-treatment ratings all significantly worse than pre-treatment ($p < 0.001$). Prevalence of clinically significant post-treatment disturbance was high by patient and family ratings (48%/66% apathy, 35%/53% disinhibition, 39%/56% executive dysfunction). Post-treatment neurobehavioral symptoms strongly correlated with lower quality of life ($r = -0.62$) and higher anxiety ($r = 0.62$) and depression scores ($r = 0.67$, all $p < 0.001$). Total MoCA scores did not correlate with RT dose. However, greater declines in apathy, disinhibition and executive dysfunction were associated with receiving >75 Gy to temporal lobes.
Conclusion: NPC treated with IMRT had moderate to high rates of neurocognitive impairment and clinically significant apathy, disinhibition, and executive dysfunction.
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Neurocognitive dysfunction occurs among cancer survivors across a broad spectrum of solid non-CNS malignancies [1–4], including head and neck cancers (HNC) [5–9]. Lee et al. presented the first series recognizing neurocognitive dysfunction following radiotherapy for nasopharyngeal carcinoma (NPC) in 1989, however, subsequently minimal progress has been made [10]. Most published series predate intensity-modulated radiotherapy (IMRT) and heavily focus on cohorts with and without temporal lobe necrosis (TLN) [7,10–18].

IMRT heralded a major advancement in HNC treatment, facilitating enhanced tumor dosing with improved normal tissue sparing [19,20]. Only a few series report neurocognitive outcomes in IMRT-treated NPC survivors [11,17,21], and although TLN, which has been a reliable marker of neurocognitive performance in historically treated cohorts [7,16] may be less frequent in the IMRT era [22], it has not been established that this translates into lower neurological morbidity.

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NPC patients can expect high rates of disease control and survival following definitive chemoradiotherapy. NPC presents younger than other HNCs, hence survivors will live with a host of persisting cancer-related symptoms for many years and any reduction in long-term neurocognitive function could have considerable long-term benefit [23,24].

This study was undertaken to determine whether long-term NPC survivors treated with IMRT are at risk of cognitive and neurobehavioral sequelae.

Materials and methods

Participants

The data presented were collected as part of a larger study reporting late toxicities in NPC survivors who were disease-free and a minimum of four years following completion of IMRT. We have reported long-term toxicity, quality of life and emotional distress outcomes in this patient cohort previously [25]. IMRT for HNC patients was implemented at our Hospital in 2004. Study accrual occurred from June 1st 2015 to June 30th 2016. Eligibility was determined from a prospectively managed institutional quality assurance system [26], and patients were invited to participate at their usual follow-up appointment. Eligible patients were $\geq$18 years at time of treatment and received curative-intent IMRT (70 Gy/35#) ± current/adjuvant cisplatin-based chemotherapy. Exclusion criteria were: (1) recurrent NPC; (2) physical or neurological conditions impacting participation; or (3) inability to understand and speak in English, Cantonese, or Mandarin. A trilingual research assistant administered assessments in patient's preferred language. The study was approved by the institutional ethics review board and was registered with ClinicalTrials.gov (NCT02597426).

Neurocognitive function

Objective assessment

Neurocognitive performance was assessed using the Montreal Cognitive Assessment (MoCA; English or Chinese version) [27]. The test yields a total score and seven domain scores: executive and visuospatial functioning, naming, memory, attention, language, abstraction and orientation (score 0–30). Patients with $\leq$12 y of education receive a bonus point.

We used a score of <23 to define neurocognitive impairment (NCI). Although earlier studies recommend <26 as indicating mild cognitive impairment [27], using the lower threshold reduces false-positives in both English and Chinese-speaking populations [28–32].

Subjective assessment

Patient-reported neurocognitive function was assessed with the "problems remembering" item of the MD Anderson Symptom Inventory – Head and Neck (MDASI-HN). The MDASI-HN consists of a 28-item questionnaire, including 13 general symptoms common to all cancer patients, 9 specific to HNC and 6 reporting the interference of symptoms with daily life (scored 0–10) [33,34]. Only the remembering item is reported in this study. A validated Chinese version is available.

Neurobehavioral assessment

Neurobehavioral function was assessed using the validated Frontal Systems Behavior Scale (FrSBe) tool [35], a 46-item questionnaire assessing three frontal behavioral domains: apathy, disinhibition and executive dysfunction. Responders rate each item "before illness" and "after illness/treatment", yielding pre- and post-treatment scores. Self- and family-rating forms are available. Raw scores are converted to normative T-scores (sex, age, and education matched) for each behavior and an overall "frontal dysfunction" score is also calculated. Higher scores indicate greater dysfunction: $\geq$65 is clinically significant; 60–64 is borderline; <60 is normal. The FrSBe has no official Chinese versions; it was translated by our in-house hospital's translation services and used on request.

Other patient-reported outcomes (PRO)

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) includes two 7-item subscales for anxiety (score 0–21) and depression (score 0–21). The HADS manual recommends scores of 8–10, 11–15 and >15 in each subscale to define borderline, probable and highly significant levels of morbidity respectively [36]. We considered scores of $\geq$11 as significant. A validated Chinese version is available.

Quality of life (QoL)

The Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N) consists of the FACT-G questionnaire comprising 27 questions from four domains (physical, social, emotional and functional) plus a 12-item module specific to HNC. The maximum score is 148. Higher scores reflect better QoL [24]. A validated Chinese version is available.

Demographic variables

Age, sex, education, employment and smoking status, alcohol intake, and performance status at enrollment were collected.

Disease and treatment variables

Initial stage, histological type, date of diagnosis and treatment, radiation dose received, number of cycles of concurrent/adjuvant chemotherapy (concurrent cisplatin, adjuvant cisplatin/5-fluorouracil) were collected. Time since treatment was calculated from the last IMRT treatment to enrollment. TLN was recorded retrospectively from all post-treatment MRI reports performed during the follow up period. Our institutional policy mandates a post-treatment MRI at 3 months, followed by 6-monthly MRI's for two years and annually thereafter to 5 years. Right temporal lobe (RTL), left temporal lobe (LTL), combined temporal lobe (CTL) and frontal lobes (FL) were contoured from fused MRI and CT images by a trained radiation therapist (BC). Absolute volumes (cc) were calculated in 5 Gy increments from 5 to 75 Gy.

Statistical analysis

Descriptive statistics were provided for baseline demographic and treatment variables as well as other continuous and categorical measures. Univariable analyses were performed with a logistic regression model for binary outcomes and linear regression for continuous scores. Multivariable models were used to assess the effect of different clinical, tumor and treatment factors on objective neurocognitive performance. Paired t-tests were conducted to assess the difference between mean FrSBe scores of pre- and post- treatment. Pearson's correlation coefficient was applied to determine correlation between two continuous variables if both variables are normally distributed. Spearman's correlation coefficient was used on non-normalized variables such as dosimetric scores. Results are considered exploratory and corrections for multiple analyses were not performed. All statistical analyses were conducted using SAS 9.4 and R (http://CRAN.R-project.org, R Foundation, Vienna, Austria).

Results

Among 128 invited patients, 102 participated in the neurocognitive component of this study. All patients completed the MoCA, while 100 patients and 32 family members completed the FrSBe, respectively. Questionnaires were reported at a median time of 7.5 years (4.1–11.1) following completion of radiotherapy.

Demographic, clinical and treatment factors and PROs are reported in Table 1. TLN was identified in 22 patients (22%). Sixty-three (62%) patients completed all assessments in English, 30 (29%) in Chinese, and 9 (9%) completed the questionnaires in English and the MoCA in Chinese.

Table 1
Baseline demographic and clinical factors ($N = 102$).

Variable	*N* (%)
Age at study	
Median(range)	56.5(32,77)
Age at diagnosis	
Median(range)	48.7(23,70)
Sex	
Male:Female	66:36(65/35)
Education level	
<High School	19(19)
Completed High School	13(13)
Some College/University	4(4)
Completed Technical School	9(9)
Completed College or University	49(48)
Professional/Post-graduate Degree	8(8)
Employment status	
Unemployed	13(13)
Retired	26(25)
Employed	63(62)
Smoking history	
Current/Ex	27(26)
Never	75(74)
Drinks per week	
0	84(82)
1–9	17(17)
10+	1(1)
ECOG	
0	59(58)
1	38(37)
2	4(4)
3	1(1)
Initial T category	
T1	33(32)
T2	15(15)
T3	31(30)
T4	23(23)
Radiation dose received	
70 Gy	101(99)
66 Gy	1(1)
Years since radiotherapy	
Median(range)	7.5(4.2,11.1)
Total chemotherapy cycles	
0	8(8)
1	0(0)
2	3(3)
3	11(11)
4	10(10)
5	37(36)
6	33(32)
Temporal lobe necrosis	
Yes:No	22:80(22/78)
FACT-H&N Total($n = 101$)	
Median(range)	107(46,148)
HADS anxiety score($n = 100$)	
Median(range)	6(0,16)
Abnormal ≥11	9(9)
HADS depression score($n = 100$)	
Median (range)	4(0,17)
Abnormal ≥11	11(11)

Neurocognitive assessment

Objective neurocognitive performance

The median MoCA score was 24 (range 13–30, mean 23.7, SD 3.4). Thirty-three (32%) patients scored in the impaired range.

Supplementary Table 1 shows univariable analysis of patient, tumor and treatment variables. Education was a strong predictor of higher performance. Moderate alcohol consumption (1–9 drinks/week) also predicted higher scores compared to either abstainers or heavy drinkers (≥10 drinks/week). No other patient, tumor or treatment factor was associated with MoCA performance. In particular, neither chemotherapy intensity, temporal lobe necrosis, nor time since completion of treatment predicted for neurocognitive performance. One patient in this series was found to have a derangement in the hypothalamic–pituitary axis; this patient scored within the normal range (25).

Subjective cognitive function

Self-reported memory problems (mean 3.1, SD 3) scored fourth highest across all MDASI-HN items. Only dry mouth, mucus and swallowing/chewing items scored higher (data not shown). On univariate analysis, better performance status and a longer time since treatment corresponded with better self-reported memory function.

Neurobehavioral assessment

Patient report

Patient self-reported results are presented in Table 2.

Ratings revealed normal pre-illness behaviors (mean scores <60). Across all domains, post-treatment scores were significantly higher ($p < 0.05$) and were in the abnormal range.

Patients reporting in the clinically significant range (≥65) was significantly higher in the post-treatment setting versus their recalled pre-illness function: FrSBe total 44% v 23%; apathy 48% v 19%; disinhibition 35% v 20%; and executive dysfunction 39% v 24% (all $p < 0.05$).

Family report

Family and paired patient results are presented in Table 3. The same pattern was observed in the subset ($N = 32$) of patients with matched family ratings. By family reports, pre-illness levels of apathy, disinhibition, and executive dysfunction were in the normal range (mean <60). Post-treatment ratings were, however, in the abnormal range with a significant increase from baseline ($p < 0.05$). Family reports showed a similar trend in the proportion of patients scoring in the clinically abnormal range in the post-treatment setting ($p < 0.05$).

There were no observable statistical differences (*t*-test) between patient- and family-reported scores in either post-treatment scores or their changes from baseline (total, all domains). However, there were some discrepancies (family reporting higher scores) in the pre-treatment setting means for the total ($p = 0.023$) and apathy ($p = 0.006$), but not for disinhibition or executive dysfunction domains ($p > 0.05$). Patient-family correlations are presented in Supplementary Table A.2.

Analyzed as either the total post-treatment score or the change in the total score, only the number of years of smoking (estimate: 1.03, 95% CI:0.17–1.89, $p = 0.019$) predicted a larger change in pre to post ratings. We observed a borderline association ($p = 0.074$) between a longer time since treatment completion and smaller changes between pre and post scores. No other demographic, clinical or treatment factor (excluding dosimetry – see below) reached significance.

Table 2
FrSBe T-scores ($N = 100$).

Parameter	Pre rating	Post rating	Diff (Post–Pre)	Pre vs. Post(patient) *p*-value
Total				
Mean(sd)	53.3(14.5)	64.7(19.4)	11.4(16)	**<0.001**
Median(Range)	52(28,90)	63(33,121)	6(-21,83)	
<60(*n*,%)	66(66)	41(41)		
60–64(*n*,%)	11(11)	15(15)		
65+(*n*,%)	23(23)	44(44)		**<0.001**
Apathy				
Mean(sd)	52.5(11.8)	65.3(18.2)	12.7(16.4)	**<0.001**
Median (Range)	50(32,81)	64(33,122)	6.5(-19,66)	
<60(*n*,%)	73(73)	39(39)		
60–64(*n*,%)	8(8)	13(13)		
65+(*n*,%)	19(19)	48(48)		**<0.001**
Disinhibition				
Mean(sd)	52.3(14)	60.2(17.6)	7.9(15.2)	**<0.001**
Median(Range)	50(24,100)	56(24,130)	3(-31,69)	
<60(*n*,%)	72(72)	53(53)		
60–64(*n*,%)	8(8)	12(12)		
65+(*n*,%)	20(20)	35(35)		**0.021**
Executive Dysfunction				
Mean(sd)	53(14.5)	60.7(17.7)	7.7(13.5)	**<0.001**
Median(Range)	51(28,88)	60(33,113)	3(-15,77)	
<60(*n*,%)	65(65)	48(48)		
60–64(*n*,%)	11(11)	13(13)		
65+(*n*,%)	24(24)	39(39)		**0.045**

Table 3
FrSBe T-scores for patients with family ratings.

	Patient $N = 32$				Family $N = 32$				
Parameter	Pre Ratings	Post Rating	Diff (Post –Pre)	Pre vs. Post (patient) *p*-value	Pre rating	Post rating	Diff (Post –Pre)	Pre vs. Post (family)*p*-value	Post family vs. Post patient *p*-value
Total									
Mean(sd)	53.5(12.5)	66.6(17.8)	13.1(15.7)	<**0.001**	59(12.2)	71.3(19.3)	12.3(12.3)	**<0.001**	0.23
Median (Range)	52.5 (36,78)	66 (36,118)	7.5 (−9,58)		59.1 (39,81.1)	71 (41,115)	9.5 (0,45)		
<60(*n*,%)	22(69)	11(34)			16(50)	10(31)			
60–64(*n*,%)	4(12)	4(12)			3(9)	2(6)			
65+(*n*,%)	6(19)	17(53)		**0.012**	13(41)	20(62)		0.219	0.66
Apathy									
Mean(sd)	52.9(10.5)	67.6(17.4)	14.6(18.1)	<**0.001**	59.4(10.5)	72.1(17)	12.7(13.7)	**<0.001**	0.22
Median (Range)	50(37,72)	65(38,114)	6(-9,66)		59.5(40.4,87.2)	69(44,112)	8.5(-3,50)		
<60(*n*,%)	24(75)	10(31)			16(50)	9(28)			
60–64(*n*,%)	2(6)	6(19)			7(22)	2(6)			
65+(*n*,%)	6(19)	16(50)		**0.002**	9(28)	21(66)		0.008	0.27
Disinhibition									
Mean(sd)	52.2(13.2)	62.9(18.8)	10.7(15.6)	<**0.001**	55.9(13.3)	64.6(17.5)	8.7(9.2)	<**0.001**	0.62
Median(Range)	51(30,78)	57(34,130)	6(-4,69)		53.5(34,84)	65.5(38,101)	4.5(0,35)		
<60(*n*,%)	21(66)	17(53)			20(62)	13(41)			
60–64(*n*,%)	5(16)	1(3)			4(12)	2(6)			
65+(*n*,%)	6(19)	14(44)		0.057	8(25)	17(53)		0.072	0.58
Executive Dysfunction									
Mean(sd)	53.5(13.4)	61.4(15.8)	8(11.3)	<**0.001**	57.7(11.9)	66.6(18.4)	8.9(10)	<**0.001**	0.17
Median (Range)	51(33,84)	62.5(33,97)	4(-10,41)		59.5(39.1,81)	68(40,120)	6.5(0,39)		
<60(*n*,%)	21(66)	13(41)			16(50)	12(38)			
60–64(*n*,%)	3(9)	5(16)			6(19)	2(6)			
65+(*n*,%)	8(25)	14(44)		0.149	10(31)	18(56)		0.109	0.40

PRO correlations

Total MoCA score did not correlate with the MDASI-HN "memory problems" question ($r = -0.15$; $p = 0.14$). Patients who performed more poorly on the MoCA showed a non-significant trend in reporting lower QoL (FACT-H&N, linear regression estimate 0.02, 95% CI:0–0.05, $p = 0.072$).

Lower QoL strongly correlated with higher neurobehavioral symptoms (total, $r = -0.62$, $p < 0.001$; apathy, $r = -0.65$, $p < 0.001$; disinhibition, $r = -0.51$, $p < 0.001$; executive dysfunction, $r = -0.51$, $p < 0.001$). Higher anxiety and depression scores also correlated moderately to strongly with higher reported neurobehavioral symptoms (all domains $r = 0.51$–0.70; all $p < 0.001$).

Dosimetric analysis

Supplementary Table A.3 summarizes significant dosimetric associations.

Objective (MoCA) and Patient-reported (MDASI-HN remembering) scores

No dosimetric factors correlated with either the total MoCA score or scoring within the impaired range. The individual domains of executive functioning, naming, memory, attention and language similarly showed no dose effect. However, significant correlations were identified in the following domains: (1) visuospatial – low and moderate doses to RTL (V10-V20), LTL (V15-V35) and CTL

(V10-V35); (2) abstraction – high doses to RTL (V75) and CTL (V75); and (3) orientation scores – low, moderate and high doses to RTL (V5, V10, V35,-V50, V75), CTL (V10, V75) and high doses to FL (V65-V75). CTL-V75 and FL-V65 correlated with greater self-reported memory problems.

Neurobehavioral scores

We did not observe a correlation between brain dosimetry and post-treatment scores (individual domains or total score). However, patient-reported changes in the FrSBe total, as well as apathy and executive dysfunction scores were associated with RTL-V75 and the combined dose to both temporal lobes (V75). Change in apathy was also associated with V75 to the LTL. A borderline significant correlation existed between RTL-V75 and disinhibition.

Discussion

To our knowledge, this series constitutes the largest report on long-term cognitive and neurobehavioral outcomes for IMRT-treated NPC survivors. Results showed that NPC survivors treated with IMRT (+/− chemotherapy) are at significant risk of both neurocognitive and neurobehavioral dysfunction.

With a median follow-up of 7.5 years, 32% of patients scored as impaired. Table 4 summarizes neurocognitive outcomes in other published NPC reports. Had we used the MoCA cut-off of 26 used in other series, we would have reported a prevalence of 70% (71/102). Although some studies have used the MoCA, direct comparison with most series is challenging given the different instruments used.

Only few neurocognitive reports in IMRT-treated patients have been published. Hsiao et al. reported worse short-term memory, language abilities, and list-generating fluency at follow-up (median 18 months, range 12–26) compared to a pre-treatment baseline assessment [17]. A cross-sectional design by Kiang et al. used a subjective PRO questionnaire (FACT-Cog) and concluded that patients with the shortest ($\leq$2.5 y) and longest (>10y) time since radiotherapy reported poorer cognitive function than did survivors between 2.5 and 10 y post treatment [21]. Other studies have not replicated a time-since-treatment relationship with objective cognitive measures [7,13,37].

Our primary objective was to determine the burden of neurocognitive and neurobehavioral changes, while secondarily attempting to identify any modifiable predictive or protective factors. While we anticipated that a number of treatment factors would correlate with objective cognitive performance, results failed to identify a significant impact by any of the likely factors, such as time since IMRT, chemotherapy intensity or TLN. Although a dose–volume relationship has been identified in some HNC and NPC series [17,37,38], other series have not seen a clear relationship [39]. Although it was not seen with the total MoCA score, a significant dose–response was observed in the visuospatial, abstraction and orientation domains. A range of doses (low, moderate and high) to the temporal lobe (and frontal lobe for orientation) accounted for worse performance in these domains. That we did not observe a change across all domains or the overall MoCA suggests that the individual substructures responsible for these cognitive functions may be differentially affected by dose. Our series, compared to others, included a relatively larger cohort of patients and our expectation was that overall neurocognitive outcomes would correlate with temporal lobe dose. The lack of a clear overall association however, does suggest that the underlying pathogenesis of neurocognitive decline in an aging cancer population is more complex than simply radiation dose alone. In addition, the MoCA is considered a cognitive screening test, so it is possible that more robust testing might have yielded significant associations [40]. This finding may also simply highlight the lack of pre-treatment assessment, as the impact of any treatment should most strongly correlate with the "change" from baseline, particularly as pre-treatment NCI may be underrecognized in HNC populations [41], although other work suggests HNC do not differ from controls on standardized neurocognitive testing before treatment [42] Although we did not contour more detailed brain substructures, such as the hippocampus, it lies within the medial temporal lobe, which lies adjacent to the region of the brain exposed to the highest level of incidental radiation dose, it would therefore be expected that our analysis would be representative of the dose to medial temporal lobe structures. "Hippocampal-sparing" guidelines have been proposed in NPC radiation planning [43] but require correlative clinical outcomes to ensure disease control is maintained.

We report the first use of the FrSBe in either NPC or HNC. Executive dysfunction [12,14,16,39] and disinhibition [14] have been previously reported in NPC and paranasal sinus patients treated prior to the IMRT era. In our IMRT-treated cohort, sobering rates of clinically significant frontal dysfunction were found, whether assessed by patients (44%) or their family members (62%). The level of dysfunction and proportion in the clinically significant range were significantly higher in the post-treatment setting, compared to recalled baseline function. There was clearly a strong correlation between frontal dysfunction and lower QoL and higher anxiety and depression scores (although the direction of effect is not known). Inherent to the FrSBe is the possibility of recall bias, owing to the lack of baseline assessment; however, the test is validated for use in this manner, as it is virtually impossible to assess pre-morbid behavior and cognitive symptoms before a cancer diagnosis. Both family and patients showed the same pattern and magnitude of difference between "pre-illness" and "present time" ratings. Furthermore, patient and family pre-illness reports were significantly correlated with one another (Supplementary Table A.2), and together these results indicate that the assessments are valid. Patient-reported pre-illness symptom levels corroborated by family-ratings also suggests that patients appear to retain insight into their frontal dysfunction, though weaker correlations in the post-treatment ratings may indicate some degree of impaired insight or recall bias wherein patients are underreporting current symptoms or family members are overreporting. It is possible that both patients and family members have similar recall bias (of undetermined direction) when reflecting on the pre-illness function, but even so, it is clear that both patients and family members feel that neurobehavioral symptoms have worsened.

There are some additional limitations in our study. Our analysis was largely exploratory, given a relatively small sample size for a large number of factors we thought had potential to impact cognitive and neurobehavioral changes. As a cross-sectional study, we could not assess individual change over time; ideally data should be captured prospectively, with a control group for comparison, a key recommendation from the International Cognition and Cancer Task Force [40]. Additionally the Chinese translation we used did not undergo re-validation. Although the FrSBe has not been widely used or validated in non-English speaking backgrounds, the majority of study patients were comfortable answering in English.

The challenge moving forward is to identify opportunities to reduce this neurocognitive burden. Optimizing the dose-sparing capabilities of IMRT while maintaining disease control is one strategy. This may also be an ideal cohort to investigate pharmacological neuroprotective agents. Our cross sectional data clearly justify the need for prospective, longitudinal studies in NPC patients undergoing curative treatment.

Following IMRT, one-third of NPC survivors met a conservative threshold for NCI. Frontal lobe dysfunction was high across all behaviors (apathy, disinhibition and executive dysfunction)

Table 4
Selected NPC neurocognitive studies.

Author	No.	FU(yrs ± SD)	Age (mean)	Dose (Gy)	IMRT (%)	NCI (%)	Dose effect	Time effect	Notes
IMRT series									
Current Study	102	7.5 (4.2–11.1)	55.5 ± 10.4	69.96 ± 0.4	100	32*	No effect	No effect	MoCA Scores 23.7 ± 3.4
Hsiao (17)	30	1.5	47.0 ± 11.6	70–72†	100	NR	Mean TL >36 Gy or V60 > 10% worse NCI	NR	Follow up: worse short-term memory, language, list-generating fluency
Mo (11)	51	1 week pre- and post-RT	40.1 ± 8.7	70–72.32†	100	NR	NR	N/A	No difference pre- and post-RT
Kiang (21)	44	Mean 5.7y (5–162 m)	55.5 ± 13.8	NR	100	NR	NR	>10y worse than 2.5-6y; ≤2.5y worse than 2.5-6y	FACT-Cog, four time cohorts: ≤2.5y, 2.5-≤6y, 6-≤10y and >10y
Non-IMRT series									
Shen (13)	78 TLN+	6.5 ± 3.9	46.8 ± 8.6	71(66–76)	37	55.1‡	NR	No effect	MoCA: 24.8 ± 3.7; lower than control or TLN-(below)
	28 TLN-	5.3 ± 3.5	47.9 ± 7.2	70(70–72)	32	7.1‡	NR	No effect	MoCA: 28.1 ± 2.0 lower than control
Tang (7)	46 TLN+§	6.0 ± 3.5	39.9 ± 15.1	70.2(68–76)	NR	NR	NR	No effect	MoCA: 21.32 ± 2.45; lower than TLN-(below)
	46 TLN-	5.7±3.1	39.7 ± 14.6	"	NR	NR	NR	No effect	MoCA: 25.98 ± 1.73
Wu (14)	40 TLN ¦	4.3 ± 2.9	48.3 ± 9.7	70.7 ± 1.6	NR	75%*	NR	NR	MoCA: 21.8 ± 5.3; lower than TLN-(below)
	40 TLN-	3.8 ± 2.6	47.3 ± 9.4	70.5 ± 2.0	NR	NR	NR	NR	MoCA: 27.2 ± 3.0;
Lee (10)	16 (control group – 21)	Mean 5.5 (2.5–10.2)	48 ± 9	59.5 (3.5 Gy/ fraction)	0%	NR	NR	NR	RT group: full scale, verbal and performance IQ lower; geometric design recall and immediate verbal recall worse; More subjective memory complaints
Lam (18)	40 TLN+ (19 controls)	5.5 ± 2.9	45.7 ± 7.2	66–71.2§	0%	NR	NR	NR	TLN + and TLN- similar, but worse memory testing than controls
	20 TLN-	5.0 ± 2.0	45.5 ± 5.6	66–71.2§	0%				
Hua (12)	27 (28 NPC awaiting RT; 35 normal controls)	1.7(mean)	45.1 ± 7.7	64.8–72.8	0%	NR	NR	NR	No difference in intellectual function; RT group worse auditory attention/concentration, recent memory, visuospatial abilities and immediate and delayed verbal recall and immediate visual recall

Abbreviations: IMRT = intensity-modulated radiotherapy; NCI = neurocognitive impairment; TLN = temporal lobe necrosis.
* Using MoCA < 23.
† range, mean not supplied.
‡ NCI defined by MoCA < 26.
§ clinical TLN was not reported.
¦ 90% ≥Grade 2 clinical symptoms.

whether reported by patients' or their family members. Further refinements in radiation delivery and studies aimed at understanding and modifying this burden are needed.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.09.012.

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