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ORIGINAL ARTICLE **CME**

Secondary Adrenal Insufficiency: A Cross-sectional Study of Nasopharyngeal Carcinoma Patients after Treatment with Intensity-modulated Radiotherapy

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ABSTRACT

Objective: *To review the incidence of secondary adrenal insufficiency (SAI) in nasopharyngeal carcinoma (NPC) patients treated with intensity-modulated radiotherapy (IMRT), and to determine the characteristics and risk factors associated with the development of SAI.*

Methods: *A total of 143 NPC patients diagnosed between 2009 and 2010 and treated with radical IMRT were retrospectively reviewed. The low-dose short Synacthen test was used to determine the presence of SAI. Using Kaplan-Meier method and Cox proportional hazard regression, the relationship between development of SAI and various clinical parameters was evaluated.*

Results: *The median follow-up period was 65 months. The median mean and median maximum doses to the pituitary gland were 56.3 Gy (range, 19.1-72.0 Gy) and 59.5 Gy (range, 28.5-73.8 Gy), respectively. The cumulative incidences of SAI at 2 and 5 years post-treatment were 7.7% and 17.5%, respectively. The median time to onset of SAI was 30.5 (range, 16-82) months after radiotherapy. Multiple Cox regression analysis revealed that receiving additional radiotherapy after a definitive course of radiotherapy was an independent risk factor for the development of SAI, with a relative risk of 6.598 (95% confidence interval = 1.554-28.013; p = 0.01).*

Conclusion: *SAI is common in NPC patients treated with IMRT. Regular monitoring of hypothalamic-pituitary–adrenal axis hormone function should start as early as 6 months to 1 year post-treatment so that treatment can be initiated early if indicated, especially in patients who have received additional radiotherapy after definitive radiotherapy for NPC.*

Key Words: *Adrenal insufficiency; Hypopituitarism; Nasopharyngeal neoplasms; Radiotherapy*

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中文摘要

繼發性腎上腺功能不全：鼻咽癌患者調強放射治療後的橫斷面研究

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目的：回顧調強放療（IMRT）治療鼻咽癌患者繼發性腎上腺皮質功能不全（SAI）的發生率，確定與SAI發生相關的特徵和危險因素。

方法：回顧分析2009年至2010年間根治性IMRT治療的143例鼻咽癌患者的臨床資料。使用低劑量短Synacthen測試來確定SAI的存在。使用Kaplan-Meier方法和Cox比例風險回歸評估SAI發展與各種臨床參數之間的關係。

結果：中位隨訪時間為65個月。垂體腺平均最大劑量和中位數最大劑量分別為56.3 Gy（範圍19.1-72.0 Gy）和59.5 Gy（範圍28.5-73.8 Gy）。治療後2年和5年SAI發生率分別為7.7%和17.5%。放療至腎上腺功能不全出現的中位時間為30.5（範圍，16-82）個月。多變量分析顯示，在放療結束後接受額外放療是發生SAI的獨立危險因素，相對風險為6.598（95%置信區間 = 1.554-28.013；p = 0.01）。

結論：SAI在調強放射治療的鼻咽癌患者中很常見。對於下丘腦－垂體－腎上腺軸激素功能的定期監測應該在治療後6個月至1年內開始，如有需要可提前開始治療，特別是在鼻咽癌明確放療後接受額外放療的患者。

INTRODUCTION

In the era of intensity-modified radiotherapy (IMRT), improved conformity of target volumes has allowed a lower dose to organs at risk (OARs) in the treatment of head and neck cancers including nasopharyngeal carcinomas (NPC). Radiation-induced adverse effects are common and increase with high doses used in conventional radiotherapy (RT).[1-3] The late adverse effects associated with RT are usually permanent. Pituitary dysfunction can occur in up to 62% of patients after 5 years.[4] It has been well documented that the degree of pituitary dysfunction depends on the radiation dose delivered to the hypothalamic-pituitary region.[1-3] Multiple hormone deficiencies increase with time and higher dose irradiation to the hypothalamic-pituitary axis.[1-4] Radiation-induced pituitary dysfunction after conventional RT has been studied in brain and head and neck tumours, usually in heterogeneous tumour cohorts.[2] The potential long latent period before the onset of hypopituitarism after RT reduces the feasibility of a prospective cohort study. In this cross-sectional study, the incidence, the time to secondary adrenal insufficiency (SAI), and the relationship between the time to SAI and various clinical factors were evaluated. This relationship may aid in decision making during treatment planning as well as post-treatment follow-up to screen for such latent adverse effects of RT so that treatment can be initiated early if indicated.

METHODS

Patients

A total of 143 consecutive patients previously treated with definitive RT for NPC between 2009 and 2010 at the Department of Oncology, Princess Margaret Hospital were retrospectively reviewed. Patients who received RT or intracranial surgery prior to the treatment of their NPC and those who had pituitary dysfunction prior to the diagnosis of NPC were excluded.

Treatment Methods

All patients received irradiation with megavoltage photons using IMRT, and they were immobilised with a thermoplastic shell from head to shoulder. Computed tomography of the head and neck region with 3-mm thick scanning intervals was used for treatment planning and imported to the treatment planning system. The attending oncologist contoured the target regions and OARs and the medical physicist or radiotherapist designed the treatment plan. The OARs included the parotid glands, brain stem, spinal cord, eyes, lenses, optic nerves, optic chiasm, cochlea, temporal lobes, and brachial plexus. The target volumes were 33 to 35 fractions (fr) over 6.5 to 7 weeks at three dose levels with simultaneous integrated boosts: clinical target

volume (CTV) 70 was defined as 70 Gy to gross tumour volume, nasopharynx, and lymphadenopathy; CTV 60 as 60 Gy to high-risk lymphatic regions; and CTV 54 as 54 Gy to low-risk lymphatic regions. The CTVs were expanded by a 5-mm margin to obtain the planning target volume (PTV).

The planning objective was that 100% of the dose would cover 95% of the PTV and the maximum dose would not exceed 107%. The maximum doses to the brain stem and spinal cord were set at 54 Gy and 45 Gy, respectively. The dose to other normal tissues was limited within a reasonable range without compromising the target volume coverage. The Eclipse Planning System (Varian Medical Systems; Palo Alto [CA], US) was used for IMRT planning with seven to nine gantry angles to evenly separate the coplanar fields. The IMRT was delivered using a Varian linear accelerator equipped with a dynamic multileaf collimator. Treatment position was verified on days 1, 2, and 3 of the treatment course and then weekly using on-board imaging.

Concurrent chemoradiotherapy was given to patients with stage II or above NPC. Regimens included cisplatin 100 mg/m^2 every 21 days for two or three cycles or weekly cisplatin 40 mg/m^2 for up to six cycles. Patients with advanced disease received adjuvant chemotherapy at the discretion of the treating oncologist following assessment of performance status. Patients who received adjuvant chemotherapy received cisplatin 80 mg/m^2 on day 1 plus fluorouracil 1000 mg/m^2 daily for 96 hours every 28 days for three cycles. Patients with locally advanced disease received induction chemotherapy at the discretion of the treating oncologist; they were largely patients with obvious intracranial invasion, large lymph nodes or cases in which treatment volume threatened a critical OAR such as the brainstem. Patients who received induction chemotherapy received cisplatin 100 mg/m^2 on day 1 plus fluorouracil 1000 mg/m^2 daily for 120 hours every 21 days for three cycles.

Tumour response was assessed 8 to 12 weeks after completion of RT. All patients underwent a complete physical examination and fibreoptic nasopharyngoscopy. Additional imaging or other laboratory tests were arranged if indicated. Persistent primary or lymph node metastasis 12 to 16 weeks after completion of RT was considered locoregional failure. Persistent disease and relapse were commonly treated by either RT, surgery, or chemotherapy. Those who received additional RT were also included for analysis. Such patients either received stereotactic radiotherapy (SRT) boost using IMRT or a second course of RT. In patients who underwent SRT, two fractionation schemes were used: 18 Gy prescribed to 90% isodose line in 3 fr and 48 Gy prescribed to 90% isodose line in 6 fr. Patients who received a second course of RT for local recurrence usually received 60 Gy/30 fr.

Follow-up

Patients were followed up regularly at 4- to 6-month intervals and pituitary hormonal function assessment was recommended annually.

Diagnosis of Secondary Adrenal Insufficiency

Adrenal function was assessed by an initial screening test with morning cortisol measured between 8 am and 10 am. If the result was less than 400 nmol/l, the patient was referred for a low-dose short Synacthen test (LDSST). The LDSST (1 μg) is more sensitive than the standard-dose (250 μg) Synacthen test in establishing a diagnosis of secondary adrenal suppression.[5] The LDSST has replaced the insulin tolerance test, previously considered the gold standard for diagnosing SAI, because it is more convenient, less labour-intensive to administer, and does not carry the risk of hypoglycaemia.[6] The LDSST was performed with pre–adrenocorticotropic hormone (ACTH) cortisol taken in the morning, followed by an intravenous bolus injection of ACTH 1 μg. Blood was sampled for cortisol measurement 30 minutes after injection. The patient was considered to have SAI if the 30-minute cortisol was <500 nmol/l in concordance with international standards.[7]

Statistics

The cumulative risk of SAI from the date of completion of initial RT was estimated by the Kaplan-Meier method. Differences in cumulative risk between groups were based on the log rank test. The Cox proportional hazards regression model was utilised to estimate the relative risk (RR) for development of SAI. All reported p values were two-sided and considered statistically significant if <0.05. This study was approved by the Research Ethics Committee of the institution.

RESULTS

Characteristics of Patients with Secondary Adrenal Insufficiency

Demographic and clinical characteristics of patients are presented in Table 1. A total of 143 NPC patients were examined, with a median follow-up period of 65

(range, 5-87) months. In all, 81 (56.6%) had had cortisol checked at least once every 2 years, 107 (74.8%) at least once every 3 years, and 130 (90.9%) had had at least one morning cortisol measured. Among 90 patients who had a morning cortisol level of <400 nmol/l, 14 (15.6%) did not proceed to LDSST. Of these 143 patients, 29 (20.3%) developed SAI as defined by a 30-minute cortisol level of <500 nmol/l in LDSST. If the cut-off of 550 nmol/l as suggested by Choi et al[6] was used, 44 (30.8%) patients would have been diagnosed with SAI (Table 2). In this study, we used 500 nmol/l as the cut-off for 30-minute cortisol in LDSST for diagnosis of SAI according to international standards. The median time to SAI was 30.5 (range, 16-82) months among the patients diagnosed to have SAI.

The majority of patients diagnosed with SAI were asymptomatic (69%). Patients who did exhibit symptoms of SAI had non-specific complaints such as dizziness (13.8%) and malaise (17.2%). One patient presented during an acute infective episode of pneumonia (Table 3). Among those SAI patients, 69% were prescribed regular hydrocortisone 10 mg daily to twice daily while 20.7% were instructed to take hydrocortisone upon acute stress, e.g. during an episode of infection (Table 4). A smaller proportion of patients (10.3%) did not stay on any hydrocortisone replacement, usually due to non-compliance or refusal.

Table 1. Patient characteristics (n = 143).

Characteristics	No. (%)	No. (%) with SAI
Gender		
Male	110 (76.9)	22 (20.0)
Female	33 (23.1)	7 (21.2)
Age, y		
Median (range)	53 (23-84)	
≤60	102 (71.3)	22 (21.6)
>60	41 (28.7)	7 (17.1)
T stage		
1	20 (14.0)	2 (10.0)
2	33 (23.1)	11 (33.3)
3	61 (42.7)	12 (19.7)
4	29 (20.3)	4 (13.8
Mean dose to pituitary gland, Gy		
Median (range)	56.3 (19.1-72.0)	
<40	34 (23.8)	9 (26.5)
40-59.9	63 (44.1)	14 (22.2)
≥60	46 (32.2)	6 (13.0)
Maximum dose to pituitary gland, Gy		
Median (range)	59.5 (28.5-73.8)	
<40	9 (6.3)	3 (33.3)
40-59.9	68 (47.6)	17 (25.0)
≥60	66 (46.2)	9 (13.6)
Concurrent chemotherapy		
No	52 (36.4)	7 (13.5)
Yes	91 (63.6)	22 (24.2)
Induction chemotherapy		
No	99 (69.2)	20 (20.2)
Yes	44 (30.8)	9 (20.5)
Adjuvant chemotherapy		
No	124 (86.7)	23 (18.5)
Yes	19 (13.3)	6 (31.6)
Nasopharyngectomy		
No	136 (95.1)	27 (19.9)
Yes	7 (4.9)	2 (28.6)
SRT or second-course RT		
No	134 (93.7)	26 (19.4)
Yes	9 (6.3)	3 (33.3)

Abbreviations: RT = radiotherapy; SAI = secondary adrenal insufficiency; SRT = stereotactic radiotherapy.

Table 2. Patients diagnosed with SAI with different LDSST cut-off values.

Cut-off value	No. (%)
≤500 nmol/l	
Yes	29 (20.3)
No	114 (79.7)
≤550 nmol/l	
Yes	44 (30.8)
No	99 (69.2)

Abbreviations: LDSST = low-dose short Synacthen test; SAI = secondary adrenal insufficiency.

Table 3. Patients with symptomatic and asymptomatic secondary adrenal insufficiency.

	No. (%)
Symptomatic	9 (31.0)
Dizziness	4 (13.8)
Malaise	5 (17.2)
Other symptoms/presentation	1 (3.4)
Asymptomatic	20 (69.0)

Table 4. Patients on hydrocortisone replacement therapy.

	No. (%)
With treatment	
Regular replacement	20 (69.0)
During acute stress episodes	6 (20.7)
Without treatment	3 (10.3)

Table 5. Patients with secondary adrenal insufficiency and hypothyroidism.

	No. (%)
Yes	
On regular replacement	5 (17.2)
Subclinical hypothyroidism	9 (31.0)
No	15 (51.7)

Besides, 48.2% of SAI patients were noted to have some degree of hypothyroidism (Table 5); most (31.0%) had subclinical hypothyroidism and some (17.2%) required thyroxine replacement.

Significant Causative Factors

The cumulative incidences of SAI were 0%, 7.7% and 17.5% at 1, 2 and 5 years, respectively (Figure). Patients who received additional RT in the form of SRT or second-course RT developed an earlier onset of SAI with cumulative incidences of 0%, 11.1% and 33.3% at 1, 2 and 5 years, respectively. Seven patients received SRT boost using IMRT to the GTV: six received 18 Gy/3 fr and one received 48 Gy/6 fr. Two patients had a second-course RT and received 60 Gy/30 fr. The estimated additional maximum biological equivalent doses to 2-Gy fr (BED_{2Gy}) calculated using an α/β of 3 for late radiation reaction in normal tissue received by the pituitary gland ranged from 2.3 to 110.8.

Multiple Cox regression analysis revealed that additional radiation to more than 70 Gy in addition to the initial radical course of IMRT in the form of SRT or second-course RT was an independent risk factor for developing SAI with a RR of 6.598 (95% confidence interval = 1.554-28.013; p = 0.01) [Table 6 and Figure].

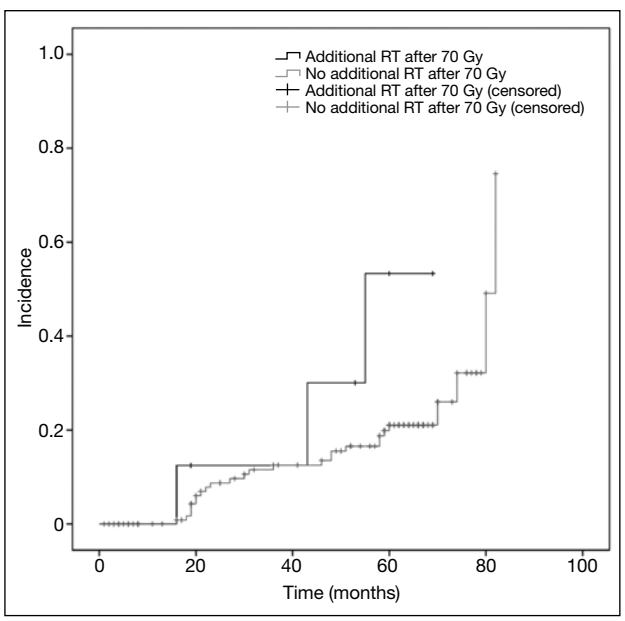

Figure. Cumulative incidence of SAI in patients who received additional radiotherapy after 70 Gy in the form of SRT boost or a second-course RT.
Abbreviations: SAI = secondary adrenal insufficiency; SRT = stereotactic radiotherapy; RT = radiotherapy.

Factors such as T stage, age, induction chemotherapy, concurrent chemotherapy, adjuvant chemotherapy, and mean or maximum dose of the initial course of RT to the pituitary gland were not found to be independent risk factors associated with the development of SAI.

DISCUSSION

SAI after definitive RT for NPC is common but can have an extended latent period. This cross-sectional study aimed to analyse the characteristics and causative factors of SAI in a group of NPC patients who received IMRT as definitive treatment with extended follow-up. In our cohort, a cumulative incidence of SAI of 17.5% was observed at 5 years. In a study conducted in the early 1990s by Lam et al,[4] pituitary dysfunction occurred in up to 62% over 5 years and SAI was seen in 26.7%. In our cohort, 20.3% and 30.8% of patients were diagnosed with SAI after IMRT using a diagnostic LDSST cut-off of 500 nmol/l and 550 nmol/l, respectively. Time to SAI evaluated using multivariate analyses revealed that additional RT after the initial definitive course with IMRT in the form of SRT boost or second-course RT was a significant risk factor for developing SAI with a RR of 6.598 (p = 0.01). With advances in RT techniques, more patients are likely to receive dose escalation in the form of SRT boost, and also a second course of radiation for locally advanced persistent disease or local relapse. With improved treatment outcomes and longer survival, long-term side-effects of RT are expected to be seen more frequently. In this study, NPC patients treated with IMRT with long-term follow-up were reviewed and enabled analyses of factors related to the development of SAI. Due to the potential extended latent period, diagnosis of the condition can be underestimated as a result of poor compliance of pituitary hormonal profile screening or delay in referral for LDSST. The true number of patients with SAI may be higher as only 56.6% of patients had their hormone levels monitored at least once every 2 years. This important complication, if left untreated, may cause refractory hypotension and even death during acute physiological stress.

In our study, 20.3% of patients were diagnosed with SAI using a LDSST cut-off of 500 nmol/l. Other studies including a local study using this cut-off value were shown to have 90% to 96% specificity and sensitivity of 61% to 100%.[5,6,8-10] If a cut-off of 550 nmol/l was used, the sensitivity could increase to 97% to 100% but the specificity would decrease to 68% to 78%[6,11]; the proportion in our cohort that would be diagnosed

Table 6. Log rank test and Cox regression model analysis for patients with SAI.

	Log rank test (p value)	Cox regression model	
		RR (95% CI)	p Value
Gender	0.797		0.884
Male			
Female		0.884 (0.356-2.197)	
Age, y	0.852		0.585
≤60			
>60		1.317 (0.490-3.545)	
T stage	0.451		0.234
1-2			
3-4		0.469 (0.135-1.634)	
Mean dose to pituitary, Gy	0.575		0.924
<40			
40-59.9		0.895 (0.255-3.142)	
≥60		0.679 (0.095-4.864)	
Maximum dose to pituitary, Gy	0.474		0.557
<40			
40-59.9		1.580 (0.347-7.716)	
≥60		0.815 (0.097-6.816)	
Concurrent chemotherapy	0.326		0.164
No			
Yes		2.213 (0.723-6.779)	
Induction chemotherapy	0.880		0.178
No			
Yes		2.054 (0.720-5.863)	
Adjuvant chemotherapy	0.189		0.154
No			
Yes		2.424 (0.718-8.176)	
Nasopharyngectomy	0.595		0.416
No			
Yes		1.880 (0.411-8.592)	
Stereotactic radiotherapy boost/second-course radiotherapy	0.079		0.011
No			
Yes		6.598 (1.554-28.013)	

Abbreviations: CI = confidence interval; RR = relative risk; SAI = secondary adrenal insufficiency.

with SAI would increase to 30.8% and they would require long-term hydrocortisone treatment. Long-term steroid treatment is known to be associated with long-term toxicities such as increased risk of cataract and hyperglycaemia. Therefore, statistical analysis was performed in concordance with the international standard using the 500 nmol/l cut-off value.

The incidence of SAI increased over the years of follow-up beginning as early as 16 months after definitive RT. Although hypopituitarism tends to present within 5 years of RT, onset can be delayed by as long as 20 years. Hence lifelong surveillance is necessary.[2,12] In our study, the cumulative incidences of SAI were 7.7% and 17.5% at 2 and 5 years, respectively. The majority of patients (69%) diagnosed with SAI were asymptomatic. Patients who did exhibit symptoms had non-specific complaints such as dizziness and malaise, and up to 50% had more than one hormone deficiency such as hypothyroidism. Hence, patients with a history of irradiation to the head and neck region should be regularly screened for pituitary hormone deficiencies during routine follow-up and upon occurrence of acute illnesses such as pneumonia. Screening should be conducted at least annually after completion of RT. Patients found to be deficient in hormone secretion should be given adequate patient education and prescribed hormone replacement therapy to prevent possible life-threatening sequelae during acute episodes of stress.

Previous studies with heterogeneous tumour types reported that a dose-dependent relationship exists between the development of radiation-induced hypopituitarism and the total dose received by the pituitary.[2,3] Littley et al[2] showed that individual fr >1.8 Gy and total doses >45 Gy were independent risk

factors for hypopituitarism. Vladyka et al[3] suggested a threshold dose of 18 Gy for ACTH and thyroid-stimulating hormone deficiencies. In conventional and IMRT RT planning for NPC, the upper border of the CTV in patients with T stage 1 and 2 disease usually includes the lower half of the sphenoid sinus while the entire sphenoid sinus is included in T stage 3 and 4 patients. We postulated that T stage could be a risk factor for the development of hypopituitarism. It was initially thought that patients with T stage 3 and 4 would have a higher frequency and earlier onset of SAI because of increased mean or maximum dose received by the pituitary gland, but T stage was not found to be a significant risk factor for developing SAI in our study. Also, multivariate analyses did not identify the mean dose or maximum dose received by the pituitary gland as an independent risk factor for the development of SAI. A median mean dose of 56.3 (range, 19.1-72.0) Gy and a median maximum dose of 59.5 (range, 28.5-73.8) Gy received by the pituitary gland in our cohort suggested that the threshold tolerance dose of 45 Gy for the pituitary gland was exceeded in the majority of NPC patients treated with IMRT, regardless of stage (Table 7). The median mean BED_{2Gy} received by the pituitary gland calculated using an α/β of 3 for late radiation reaction in normal tissue in our cohort was 88.5 (range, 22.6-140.9).

Cox regression analysis indicated that additional RT after the initial definitive course with IMRT in the form of SRT or second-course RT was a significant risk factor for developing SAI with a RR of 6.598 ($p = 0.01$). In our cohort, various doses and fractionations of additional RT were given including 18 Gy/3 fr, 48 Gy/6 fr, and 60 Gy/30 fr. The additional maximum BED_{2Gy} calculated using an α/β of 3 for late radiation reaction in normal tissue received by the pituitary gland ranged from 2.3 to 110.8. SRT or second-course RT would increase the cumulative dose received by the pituitary gland, therefore increasing the risk of hypopituitarism and SAI.

Table 7. Median mean and median maximum doses received by the pituitary gland according to different T stages in the patient cohort.

T stage	Median mean dose, Gy	Median maximum dose, Gy
1	34.561 (19.194-65.878)	45.655 (33.745-71.367)
2	38.643 (19.115-59.459)	47.647 (28.514-63.679)
3	57.586 (21.316-71.963)	60.925 (39.062-73.767)
4	66.894 (41.079-72.007)	70.137 (42.080-73.538)
All stages	56.349 (19.115-72.007)	59.464 (28.514-73.767)

Previous studies have shown that shielding of the pituitary gland can reduce the risk of hypopituitarism without decreasing the efficacy of treatment.[13] In the era of IMRT, it would be interesting to explore the feasibility of reducing the dose to the pituitary gland by assigning the pituitary gland as a planning OAR in early-stage NPC receiving IMRT.

The nature of this cross-sectional study may lend itself to selection bias because the patients accrued were more likely to have complications detected. Different attending oncologists contoured the target volumes and OARs for different patients, and different medical physicists or radiotherapists designed the treatment plan for different patients. These may result in inter-operator variations in the contouring and planning of RT. The lack of strict adherence to annual pituitary hormone assessment and the delay in performing a confirmatory LDSST immediately after a positive morning cortisol test due to delay in endocrine follow-up may result in a temporal delay in the diagnosis of SAI. A prospective cohort study is warranted to define the true incidence of radiation-induced SAI, but the long latency of onset will necessitate multiple hormone assays during prolonged follow-up of a large cohort of patients.

CONCLUSION

Radiation-induced SAI is a common late complication in patients with NPC treated by IMRT. The incidence increases with long-term follow-up and the presentation can be non-specific. Patients who received additional RT in the form of SRT or a second-course RT leading to cumulative doses above 70 Gy were at a higher risk of developing SAI. Regular pituitary hormone function surveillance should be conducted during routine follow-up, at least annually, and early treatment should be initiated if indicated.

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