

# MRI of the Hypothalamus and Pituitary Gland in Patients with Hyperprolactinaemia Following Radiotherapy for Nasopharyngeal Carcinoma

K Y Lau, W T Fung, P O Chan, W M Sze, A W M Lee, T K Yau

## ABSTRACT

**Purpose:** Neuroendocrine dysfunction is a known complication of cranial radiation. While growth hormone deficiency is the most common laboratory finding, hyperprolactinaemia is one of the most common symptomatic dysfunction in adult female patients with nasopharyngeal carcinoma (NPC) following radiotherapy. This analysis aims to study the magnetic resonance imaging (MRI) features of the hypothalamus and the pituitary gland in affected patients.

**Methods:** MRI was performed in 24 patients NPC with hyperprolactinaemia detected 10-52 months following one course of radical radiotherapy. The region of study included the nasopharynx, the hypothalamus and the pituitary gland in 20 patients, while in the remaining four patients, this was limited to the pituitary gland. The estimated radiation dose to the hypothalamus and the pituitary gland was 66 Gy, and six patients also had adjuvant chemotherapy. There was no clinical evidence of tumour recurrence in all 24 patients when hyperprolactinaemia was detected.

**Results:** None of the 24 patients showed any MRI evidence of structural abnormality in the hypothalamic-pituitary region.

**Conclusion:** MRI did not reveal any structural abnormality in the hypothalamic-pituitary region of patients who developed hyperprolactinaemia following radiotherapy for NPC.

**Keywords:** Magnetic resonance imaging, Nasopharyngeal carcinoma, Hyperprolactinaemia, Radiation-induced complication

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## INTRODUCTION

For patients with cranial or head and neck tumours treated by radical radiotherapy, the hypothalamic pituitary region may inevitably receive high dose of radiation. Endocrine dysfunction is thus a known

complication with incidence ranging from 8-50%<sup>(1-7)</sup>. Growth hormone deficiency is often the first deficiency to occur both in children<sup>(8,9)</sup> and adults<sup>(6,10)</sup>. Impaired gonadotropin secretion<sup>(1,11)</sup>, delayed thyroid stimulating hormone (TSH) response to thyroid releasing hormone (TRH)<sup>(12,13)</sup> and hyperprolactinaemia<sup>(4,14)</sup> may also occur and frequently lead to symptomatic dysfunction.

The exact site of damage remains controversial. Basing on the pattern of endocrine changes, it has been suggested that the pituitary failure in patients with nasopharyngeal carcinoma (NPC) might be secondary to radiation damage of the hypothalamus and/or the hypothalamo-portal circulation<sup>(15-17)</sup>. However, previous studies using computerised tomography (CT) failed to show supporting evidence of structural damage in the corresponding site.

Magnetic resonance imaging (MRI) is more sensitive than CT in detection of hypothalamic-pituitary pathology<sup>(18-21)</sup>, but thus far there is no report on its value in investigating endocrine dysfunction induced by radiotherapy for NPC. Following is our experience in using MR to search for the site of structural damage in NPC patients who developed hyperprolactinaemia.

## METHODS

From January 1994 to October 1997, 330 adult patients (250 males and 80 females) with nasopharyngeal carcinoma (NPC) were treated with radical radiotherapy in the Department of Clinical Oncology at the Pamela Youde Nethersole Eastern Hospital (Hong Kong). The serum prolactin, free thyroxin (T4), thyroid stimulating hormone (TSH) and spot cortisol levels were routinely checked before commencement of radiotherapy and then annually during subsequent follow-up.

Hyperprolactinaemia was detected in 24 patients: 18 females and 6 males. Their age ranged from 24-62 years (mean = 41 years). Initial staging of these affected patients: nine stage II, seven stage III and eight stage IV by UICC staging classification<sup>(22)</sup>. None had any magnetic resonance imaging (MRI) or computed tomography (CT) evidence of pituitary erosion before radiotherapy, and none had tumour recurrence up

Department of  
Radiology  
Pamela Youde  
Nethersole Eastern  
Hospital  
3 Lok Man Road,  
Chai Wan  
Hong Kong

K Y Lau, MBBS,  
FRCR, DABR(DR)  
Consultant

W T Fung, MBBS,  
FRCR  
Senior Medical Officer

P O Chan, BSC,  
PD, MBA  
Radiographer

Department of  
Clinical Oncology

W M Sze, MBChB,  
FRCR  
Senior Medical Officer

A W M Lee, MBBS,  
FRCR  
Chief of Service

T K Yau, MBBS,  
FRCR  
Consultant

**Correspondence to:**  
Dr K Y Lau  
Tel: (852) 2595 6169  
Fax: (852) 2515 3194  
Email: drkylau@  
yahoo.com

**Table I. Summary of 24 patients with hyperprolactinaemia.**

Sex	Age	Stage	Symptoms	Serum Level (mIU/L)	Latency to detection (months)	Interval To MRI (months)	MRI Study	Chemotherapy
F	41	II	Amenorrhoea	891	20	30	1	
F	48	II		750	22	30	1	
M	37	II		652	29	34	1	
F	32	II	Oligomenorrhoea	1848	33	39	3	
F	39	II	Amenorrhoea	933	36	42	3	
F	40	II		4310	39	46	2	
F	28	II		1027	41	49	2	
F	44	II		805	26	34	1	
F	41	II	Amenorrhoea	2210	49	51	1	
F	52	III	Irregular cycles	1678	24	26	3	
F	31	III	Secondary Infertility	934	35	40	2	Neoadjuvant
F	45	III		985	36	44	1	
F	36	III		1081	38	39	1	
F	36	III		957	51	53	1	
M	51	III		2333	41	47	1	
M	43	III		896	43	45	1	
M	46	IVa		1818	10	27	2	Concurrent/adjuvant
F	42	IVa		1597	52	54	2	
F	37	IVa	Amenorrhoea	3319	13	27	1	Concurrent
M	52	IVa		1043	22	26	3	
M	62	IVb		663	25	34	1	Adjuvant
F	31	IVb		1409	29	31	1	Concurrent/adjuvant
F*	42	IVb	Irregular cycles	972	38	44	1	Adjuvant
F	24	IVb		995	44	50	1	

Latency = interval from completion of radiotherapy to date of detecting hyperprolactinaemia;

Interval = interval from completion of radiotherapy to date of performing MRI;

MRI studies: 1 = nasopharynx + pre- and post-gadolinium pituitary

2 = nasopharynx + post-gadolinium pituitary

3 = pituitary only

\*brachytherapy in addition to the basic course of radiotherapy

to the time of detection of hyperprolactinaemia. Furthermore, none had antihypertensive, antipsychotic, antidepressant treatment or other associated disease that required cranial therapy.

All 24 patients had a complete course of external radiotherapy using 6 MV photon from linear accelerator. The estimated dose to the hypothalamus and the pituitary gland was 66 Gy. One patient with stage IV disease had additional boost by brachytherapy (20 Gy in 4 doses), estimated additional dose to the pituitary gland was 3.5 Gy. Six patients (one stage III and five stage IV) were also given chemotherapy: two with concurrent/adjuvant, one concurrent alone, one neoadjuvant and two adjuvant. Cisplatin was used for concurrent treatment, while a combination of cisplatin and 5-fluorouracil was used for non-concurrent treatment.

Interval from completion of radiotherapy to performance of MRI ranged from 26-54 months (mean = 39 months). All 24 patients had MR done by a 1.5-T MR imaging system (Signa, GE Medical Systems, Milwaukee, Wisconsin, USA) with head coil. Both the nasopharynx and the hypothalamic-pituitary regions were investigated in 20 patients in

order to exclude tumour recurrence. The axial sections were set at 3 mm thickness and 1 mm spacing, while the coronal sections were set at 4 mm thickness and 1 mm spacing. All patients had sagittal T1 weighted localiser images, axial T1, T2 with fat saturation, coronal T1, post-gadolinium axial and coronal T1 with fat saturation for the nasopharynx, and post-gadolinium sagittal and coronal T1 for the pituitary gland. In addition, 14 of them also had pre-gadolinium sagittal and coronal T1 for the pituitary gland, one had pre-gadolinium coronal T1 for the pituitary and one had post gadolinium coronal dynamic scan for the pituitary.

In the remaining four patients, the examination was confined to the pituitary gland. Both sagittal and coronal images were set at 3 mm thickness and zero spacing. All four patients had pre- and post-gadolinium sagittal and coronal T1 weighted images of the pituitary gland, only one had additional coronal T2 weighted images of the pituitary gland.

## RESULTS

Altogether 24 of 330 patients (7.3%) with NPC treated during the period January 1994 to October 1997

developed hyperprolactinaemia following radical radiotherapy. The four-year actuarial rate was 12%. The incidence was significantly higher among female patients than male patients: 33% vs 4.8%,  $p < 0.0001$ . Table I summarises the characteristic features of these 24 patients. All male and 10 female patients were asymptomatic, while four female patients presented with amenorrhoea, one oligomenorrhoea, two irregular cycles, and one secondary infertility. Physical examination and nasopharyngoscopy did not reveal any sign of tumour recurrence, visual field defect or other signs of hormonal dysfunction.

Latent period from completion of radiotherapy to detection of hyperprolactinaemia ranged from 10-52 months (mean = 33 months). The serum level of prolactin of these 24 patients ranged from 652-4310 mIU/L (the overall mean = 1421 mIU/L). The mean level was 1483 mIU/L among the female patients (normal range being 8-656 mIU/L), and 1234 mIU/L among the male patients (normal range being 38-555 mIU/L).

None of the patients had abnormal level of free thyroxin (T4), thyroid stimulating hormone (TSH) or spot cortisol. Four stage IV patients had other radiation-induced complication: three being neck fibrosis and one hearing impairment. One stage III patient had hearing impairment.

All the MRI studies done in these 24 patients did not reveal any abnormality. There was no MR evidence of tumour recurrence, pituitary erosion, pituitary macro/microadenoma, hypothalamic lesion or temporal lobe necrosis.

## DISCUSSION

Nasopharyngeal carcinoma (NPC) is a common malignant tumour in Southern China. In Hong Kong, NPC ranked fourth for males and eighth for females in terms of incidence, and it ranked sixth for males and eleventh for females in terms of cancer deaths<sup>(23)</sup>. Radiotherapy is the primary treatment of choice, while chemotherapy is increasingly used as an adjunctive therapy for advanced cases<sup>(24,25)</sup>. The hypothalamus and the pituitary gland are exposed to high dose radiation, especially with conventional techniques of radiotherapy<sup>(1,2)</sup>. Disturbances in hypothalamic-pituitary function affecting multiple hormones were observed as early as one year after radiotherapy<sup>(2)</sup>.

The incidence of endocrine deficiency varies widely depending on the target population, the duration of follow-up and the intensity of search (including use of stimulation tests). In the study by Samaan NA et al on NPC and paranasal sinus tumour<sup>(4)</sup>, 39% (43/110) patients surviving one to 26 years following radiotherapy developed hyper-

prolactinaemia<sup>(4)</sup>. Focusing on patients  $\leq 50$  years of age with stage I NPC, Lam KSL et al<sup>(2,6)</sup> showed that 14% developed hyperprolactinaemia within two years of radiotherapy. The current study includes adult patients of all ages with NPC in all stages. Using simple investigation of serum prolactin, free thyroxin (T4), thyroid stimulating hormone (TSH) and spot cortisol, without specific stimulation tests or growth hormone assay, hyperprolactinaemia was the most common endocrine abnormality with a crude incidence 7.3% and four-year actuarial rate 12%. The latency varied widely from 10 to 52 months after radiotherapy.

In agreement with the study by Lam KSL et al<sup>(2,6)</sup>, the incidence was significantly higher in female than male patients: 33% versus 4.8%,  $p < 0.0001$ . Seven of the female patients (39%) presented with menstrual disturbances and one female patient (0.06%) presented with secondary infertility, while male patients were generally asymptomatic. The exact reason for this difference by sex is yet unknown. There was no statistical significant correlation between hyperprolactinaemia and other factors including age of the patient, the stage of disease and the use of adjuvant chemotherapy. However, it should be noted that two patients with shortest latency (10 months and 13 months) were both stage IVa cases given concurrent chemotherapy. The possibility that such chemotherapy augments the effect of radiation leading to increased risk of damage cannot be excluded.

The exact site and mechanism of damage remains controversial. Suggested possibilities include direct injury to the cells responsible for hormonal secretion, or indirect injury to the stroma, microvasculature, or vascular channels that transfer the hypothalamic hormones to the pituitary<sup>(3)</sup>. Samaan NA et al favoured primary organ damage, but no radiological evidence of structural damage could be demonstrated by conventional tomogram of the pituitary region<sup>(4)</sup>.

Other studies showed that the hypothalamus is more sensitive to irradiation than the anterior pituitary gland in both rats<sup>(15)</sup> and humans<sup>(26)</sup>. Deficiency of posterior pituitary hormone (e.g. diabetes insipidus) had not been detected in any NPC patients<sup>(12,26)</sup>. Basing on the pattern of endocrine abnormalities, Lam KSL et al<sup>(26)</sup> suggested that the endocrine impairment was most likely due to alternations in the secretion of hypothalamic releasing hormone resulting from radiation-induced damage to the hypothalamus. Therefore, hyperprolactinaemia could have resulted from injury to the hypothalamic prolactin-inhibitory factor (PIF) - producing cells<sup>(27)</sup>. However, high-resolution CT scans (GE-8800 CT scanner) failed to reveal any evidence of structural changes in the hypothalamic-pituitary region or destruction of the sella turcica<sup>(2,6)</sup>.

There is little controversy that MRI is more sensitive than conventional or computerised tomography in detection of hypothalamic-pituitary pathology<sup>(18-21)</sup>. However, in the current investigation in 24 consecutive NPC patients with hyperprolactinaemia following radiotherapy, none showed any MR evidence of tumour recurrence, pituitary erosion, pituitary macro- or microadenoma, hypothalamic lesion or other complication such as temporal lobe necrosis. The drawbacks of our study are that the protocol of MRI was not unified and coronal T2 weighted images of the pituitary gland were performed only in one patient. Although MRI is a sensitive imaging technique in the detection of hypothalamic pituitary lesion, it still has limitation in resolution to detect structural lesion. The radiation damage may be undetectable by MRI, but could be enough to affect the PIF-producing cells. The damage is possibly at cellular or microscopic level, and more detailed evaluation and further study are needed. Whether MR spectroscopy/functional pituitary imaging will be useful for further substantiation of hypothalamic pituitary axis in post-radiation hyperprolactinaemia or not requires further investigation.

In summary, hyperprolactinaemia is a common complication following radical radiotherapy for NPC and female patients are especially more susceptible. Long term follow-up with careful monitoring of all survivors is recommended. The degree of elevation of serum prolactin is unpredictable and possibly related to individual susceptibility. Adjuvant chemotherapy, especially for patients with advanced diseases, may have shorter latency. The exact mechanism of damage remains uncertain as there was no MR evidence of structural lesion in the hypothalamic-pituitary axis. This definitely does not exclude the presence of hypothalamic-pituitary damage and the study does not remove the possibility of damage at a cellular level that is below the resolution of MRI. Further protection of normal structures by conformal technique should be attempted.

## REFERENCES

- Huang Ko-En. Assessment of hypothalamic-pituitary function in women after external head irradiation. *J Clin Endocrinol & Metab* 1979; 49:623-7.
- Lam KSL, Ho JHC, Lee AWM, Tse VKC, Chan PK, Wang C, et al. Symptomatic hypothalamic-pituitary dysfunction in nasopharyngeal carcinoma patients following radiation therapy: retrospective study. *Int J Radiation Oncology Biol Phys* 1987; 13:1343-50.
- Constine LS, Woolf PD, Cann D, Mick G, McCormick K, Raubertas RF, et al. Hypothalamic pituitary dysfunction after radiation for brain tumours. *N Engl J Med* 1993; 328:87-94.
- Samaan NA, Vieto R, Schultz PN, Maor M, Meoz RT, Sampiere VA, et al. Hypothalamic, pituitary and thyroid dysfunction after radiotherapy to the head and neck. *Int J Radiat Oncol Biol Physiol* 1982; 8:1857-67.
- Samaan NA, Schultz PN, Yang KP, et al. Endocrine complications after radiotherapy for tumours of the head and neck. *J Lab Clin Med* 1987; 109:364-72.
- Lam KSL, Tse VKC, Wang C, Yeung RTT, Ho JHC. Effects of cranial irradiation on hypothalamic pituitary function – a 5-year longitudinal study in patients with nasopharyngeal carcinoma. *Q J Med* 1991; 78:165-76.
- Bajorunas DR, Ghavimi F, Jereb B, Sonenberg M. Endocrine sequelae of antineoplastic therapy in childhood head and neck malignancies. *J Clin Endocrinol Metab* 1980; 50:329-35.
- Pomarede R, Czernichow P, Zucker JM, Schlienger P, Haye C, Rosenwald JC, et al. Incidence of anterior pituitary deficiency after radiotherapy at an early age: study in retinoblastoma. *Acta Paediatr Scand* 1984; 73:115-9.
- Shalet SM, Beardwell CG, Pearson D, Morris Jones PH. The effect of varying doses of cerebral irradiation on growth hormone production in childhood. *Clin Endocrinol-Oxf* 1976; 5:287-90.
- Littley MD, Shalat SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumours in adults. *Q J Med* 1989; 262:145-60.
- Rappaport R, Brauner R, Czernichow P, Thiband E, Renier D, Zucker JM, et al. Effect of hypothalamic and pituitary irradiation on puberty development in children with cranial tumours. *J Clin Endocrinol Metab* 1982; 54:1164-8.
- Lam KSL, Tse VKC, Wang CCL, Ma JTA, Yeung RTT, Ho JHC. Endocrine function in patients with nasopharyngeal carcinoma after external irradiation to the head and neck region. *Proc R Coll Physicians Edinburgh* 1985; 15:185-6.
- Grossman A, Cohen BL, Charlesworth M, Plowman PL, Rees LH, Wass JAH, et al. Treatment of prolactinomas with mega-voltage radiotherapy. *Br Med J* 1984; 288:1105-9.
- Ahmed SR, Shalet SM. Hypothalamic growth hormone releasing factor deficiency following cranial irradiation. *Clin Endocrinol-Oxf* 1984; 21:483-8.
- Tobias CA, Lawrence JH, Born JL, McCombs RK, Roberts JE, Anger HO, et al. Pituitary irradiation with high-energy proton beams: a preliminary report. *Cancer Res* 1958; 18:121-34.
- Lawrence AM, Pinsky SM, Goldfine ID. Conventional radiation therapy in acromegaly: A review and reassessment. *Arch Intern Med* 1971; 128:369-77.
- Goldfine ID, Lawrence AM. Hypopituitarism in acromegaly. *Arch Intern Med* 1973; 132:836-9.
- Johnson MR, Hoare RD, Cox T, Dawson JM, Maccabe JJ, Llewelyn DE, et al. The evaluation of patients with a suspected pituitary microadenoma: computer tomography compared to magnetic resonance imaging. *Clin Endocrinol-Oxf* 1992; 36:335-8.
- Zucchini S, di Natale B, Ambrosetto P, De Angelis R, Cacciari E, Chiumello G. Role of magnetic resonance imaging in hypothalamic-pituitary disorders. *Horm Res* 1995; 44 suppl 3:8-14.
- Tripathi S, Ammini AC, Bhatia R, Gupta R, Berry M, Sarkar C, et al. Cushing's disease: pituitary imaging. *Australas Radiol* 1994; 38:183-6.
- Escourolle H, Abecassis JP, Bertagna X, Guilhaume B, Pariente D, Derome P, et al. Comparison of computerised tomography and magnetic resonance imaging for the examination of the pituitary gland in patients with Cushing's disease. *Clin Endocrinol-Oxf* 1993; 39:307-13.
- Wittekind C. UICC (International Union Against Cancer). TNM Classification of Malignant Tumours. Fifth edition. A John Wiley & Sons, Inc. publication. 1997; 30-2.
- Foo W. Cancer incidence and mortality in Hong Kong 1995-1996; p20.
- Cvitkovic E. International Nasopharynx Cancer Study Group: VUMCA I Trial. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (Cisplatin, Epirubicin, Bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (>=N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. *Int J Radiation Oncology Biol Phys* 1996; 35:463-9.
- Al-Sarraf M, LeBlanc M, Shanker Giri PG, Fu KK, Cooper J, Vuong Te, et al. Chemotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized intergroup study 0099. *J of Clinical Oncology* 1998; 16:1310-7.
- Lam KSL, Tse VKC, Wang C, Yeung RTT, Ma JTC, Ho JHC. Early effects of cranial irradiation on hypothalamic-pituitary function. *J of Clin Endocrinol & Metab* 1987; 64:418-24.
- Gates RB, Friesen H, Samaan NA. Inappropriate lactation and amenorrhoea: pathological and diagnostic consideration. *Acta Endocrinol* 1973; 22:101-4.