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# Endocrine Complications Following Radiotherapy and Chemotherapy for Nasopharyngeal Carcinoma

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## 1. Introduction

Long-term endocrine disorders are the most frequent complications in survivors of adult and paediatric nasopharyngeal carcinoma (NPC). The hypothalamic-pituitary (h-p) axis lies within the field of radiation therapy for NPC. Consequently, neuro-endocrine abnormalities due to radiation-induced damage of the h-p occur in the majority of patients followed long term. Similarly, radiation injury to the thyroid gland can result in primary thyroid dysfunction, particularly hypothyroidism as well as benign and malignant thyroid nodule. Chemotherapy-induced gonadal damage is another frequently seen complication in patients treated with chemotherapy.

Most of the endocrine complications are irreversible and progressive in nature. They may be of sufficient severity to have adverse impact on growth and pubertal development (in children), body image, sexual function, fertility, muscular and skeletal health and ultimately quality of life. It is mandatory that survivors of NPC undergo regular clinical, radiological and/or hormonal surveillance to ensure early diagnosis of these complications and appropriate and timely introduction of hormone replacement therapy and other therapeutic interventions.

## 2. Radiation-induced hypothalamic-pituitary dysfunction

### 2.1 Pathophysiology

Radiation damage is a potent cause of hypothalamic-pituitary (h-p) axis dysfunction. Deficiency of one or more of the anterior pituitary hormones may occur following radiotherapy for tumours of the head and neck when the h-p axis falls within the field of radiation. The pathophysiology of radiation-induced damage remains poorly understood. Neuronal cell death and degeneration due to the direct effects of radiation appear to play a major role (Hochberg et al., 1983); however, vascular damage has also been proposed (Chieng et al., 1991).

The onset and severity of radiation-induced hypopituitarism is primarily determined by the total radiation dose, the fraction size and the time allowed between fractions for tissue

repair (duration of the radiation schedule) (Thames & Hendry, 1987; Littley et al., 1989a). Radiation schedules utilising the same total dose administered over a shorter duration (larger fraction size) inflict more damage to the h-p axis. To minimise the damage to healthy neuronal tissues (including h-p axis), most radiation schedules have not used more than 2 Gy per fraction and no more than 5 fractions per week. Increasing the fraction size above 2 Gy per fraction (for the same total dose) can induce relatively more injury to the late responding (neuronal) than the early responding (tumour) tissues (Withers, 1994).

Intensive external fractionated radiotherapy in doses exceeding 60 Gy remains the primary treatment for NPC. The radiotherapy field normally covers the nasopharynx and both sides of the neck. The h-p axis is routinely included in the irradiated volume. Consequently, the rate and intensity of neuro-endocrine disturbances complicating treatment of NPC far exceed that seen following less intense therapeutic radiation schedules (18-45 Gy) used for the treatment of brain tumours or haematological malignancies. With modern technological advances in computed tomography and magnetic resonance imaging, it has become possible to use conformal radiotherapy to deliver a higher radiation dose to the main bulk of the tumour while sparing the important nearby structure to reduce long-term complications (Wei, 2001). In addition, shielding the pituitary gland during radiotherapy has been shown to reduce disturbances in pituitary function without compromising tumour control (Sham et al., 1994).

The nature of the neuro-endocrine disturbance following h-p axis irradiation is also determined by the differential radiosensitivity of hypothalamic-pituitary function. This has been shown in animal models (Hochberg et al., 1983; Robinson et al., 2001) and reflected in clinical observations in irradiated patients. Epidemiological studies reveal that the growth hormone (GH) axis is the most radiosensitive followed by the gonadotrophin (FSH & LH), adrenocorticotrophic hormone (ACTH) and thyroid stimulating hormone (TSH) axes (Clayton & Shalet, 1991; Constine et al., 1993; Duffner et al., 1985; Lam et al., 1991; Littley et al., 1989a) (Figures 1 & 2).

Low radiation doses of less than 40 Gy mostly affects the most vulnerable GH axis in isolation resulting in variable degrees of GH deficiency (Clayton & Shalet, 1991; Constine et al., 1993; Duffner et al., 1985; Littley et al., 1989a). Deficiencies of other anterior pituitary hormones start to occur when the total radiation dose delivered to the h-p axis exceeds 40 Gy, but much less frequently than GH deficiency. Panhypopituitarism is mostly seen following intensive irradiation with doses exceeding 60 Gy, typically used for the treatment of nasopharyngeal carcinoma and skull base tumours (Chen et al., 1989; Lam et al., 1991; Pai et al., 2001; Samaan et al., 1987, 1982). In contrast, posterior pituitary dysfunction with diabetes insipidus has not been reported even after the most intensive irradiation schedules (Pai et al., 2001).

With less intensive radiation schedules utilising doses of less than 40 Gy, it would appear that age at irradiation influences differential impact on various h-p axes susceptibility to radiation damage. The somatotrophic (GH) axis is more vulnerable to radiation damage in children than adults, while the ACTH axis seems to be more vulnerable to damage in adults than children. These conclusions are based on the relative frequencies of various anterior pituitary hormones deficiencies reported with various radiation schedules, with a dose range of 18-50 Gy, administered to children and adults for non-pituitary brain tumours and

leukaemia. For example, isolated GH deficiency is frequently seen in children who received radiation doses of less than 24 Gy (Ogilvy-Stuart et al., 1992) but none in the adults (Littley et al., 1991). In a study of 56 patients irradiated for non-pituitary brain tumours in adulthood, Agha et al (Agha et al., 2005) reported variable degrees of hypopituitarism in 41% of patients. In this study (Agha et al., 2005), GH deficiency (32%) was less frequent than that reported in irradiated children (Clayton & Shalet, 1991; Livesey et al., 1990; Samaan et al., 1987), but ACTH (21%), TSH (9%) and gonadotropin (27%) deficiencies were relatively more common than or similar to that reported in cancer survivors irradiated during childhood (Constine et al., 1993; Livesey et al., 1990; Samaan et al., 1987). The differential influence of age is less clearly defined with intensive irradiation, but it appears to follow the same pattern. Samaan et al (Samaan et al., 1987) in their study of 166 patients aged 6-80 years, who had received high dose irradiation for NPC, showed that children younger than 15 years of age had a higher incidence of GH deficiency soon after radiotherapy than older patients; however, the older age group showed more adrenocortical and luteinizing hormone deficiency.

Irrespective of the intensity of radiation schedule, radiation-induced h-p dysfunction is also time dependent. Both increased incidence and severity of hormonal deficits are seen with longer post-irradiation follow-up intervals (Achermann et al., 2000; Clayton & Shalet, 1991; Lam et al., 1991; Littley et al., 1989b; Samaan et al., 1987; Schmiegelow et al., 2000) (Fig 1 & 2). Secondary pituitary atrophy consequent upon lack of hypothalamic releasing/trophic factors accounts for the progressive nature of the hormonal deficits, in addition, to the delayed direct effects of radiotherapy on the axis. There is a belief that radiation may cause delayed brain tissue damage and dysfunction through chronic inflammation and/or enhanced release of proinflammatory cytokines (Chiang et al., 1997; Kyrkanides et al., 1999). The delayed direct radiation damage to the pituitary gland is supported by the gradual decline in the elevated prolactin levels seen in some patients after prolonged periods of follow up post radiotherapy (Littley et al., 1989a).

The predominant site of radiation damage, pituitary vs. hypothalamic, has attracted some controversy. Contrary to what had been believed that the hypothalamus is more radiosensitive than the pituitary and that hypothalamic damage predominates following less intensive radiation schedules (<50 Gy), recent studies by the author et al (Darzy et al., 2005, 2006, 2007, 2009) have strongly suggested the opposite with robust evidence that direct radiation-induced damage to the pituitary still occurs even with low radiation doses and that the pituitary may be the predominant site of radiation damage. However, with higher range of conventional irradiation, i.e. doses in excess of 60 Gy, there is robust clinical evidence to suggest that intensive radiotherapy inflicts dual damage to both the pituitary as well as the hypothalamus resulting in early multiple anterior pituitary hormone deficiencies (Chen et al., 1989; Lam et al., 1991; Pai et al., 2001; Samaan et al., 1982). In addition to direct hypothalamic damage, neuropharmacological studies have suggested that radiation-induced hypothalamic dysfunction may be secondary to radiation damage of the suprahypothalamic neurotransmitter pathways (Jorgensen et al., 1993; Ogilvy-Stuart et al., 1994). Radiation-induced changes at cellular and molecular levels most certainly play a role in the dysfunction of the irradiated h-p axis.

Pituitary damage is demonstrated by impaired GH, LH/FSH, and TSH responses to direct stimulation with exogenous GHRH, LHRH or TRH, respectively. Hypothalamic damage, on

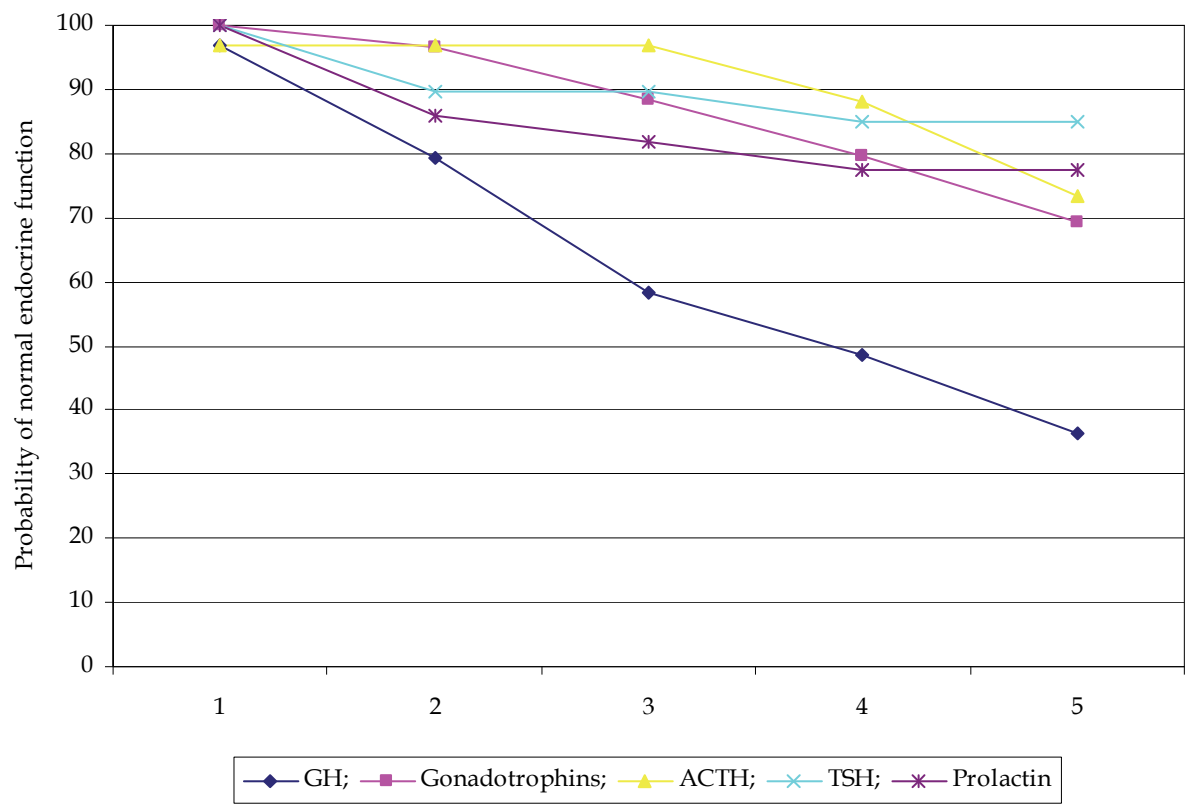


Fig. 1. Cumulative probability of normal endocrine function following radiotherapy for nasopharyngeal carcinoma. Adapted from Lam et al 1991, with permission.

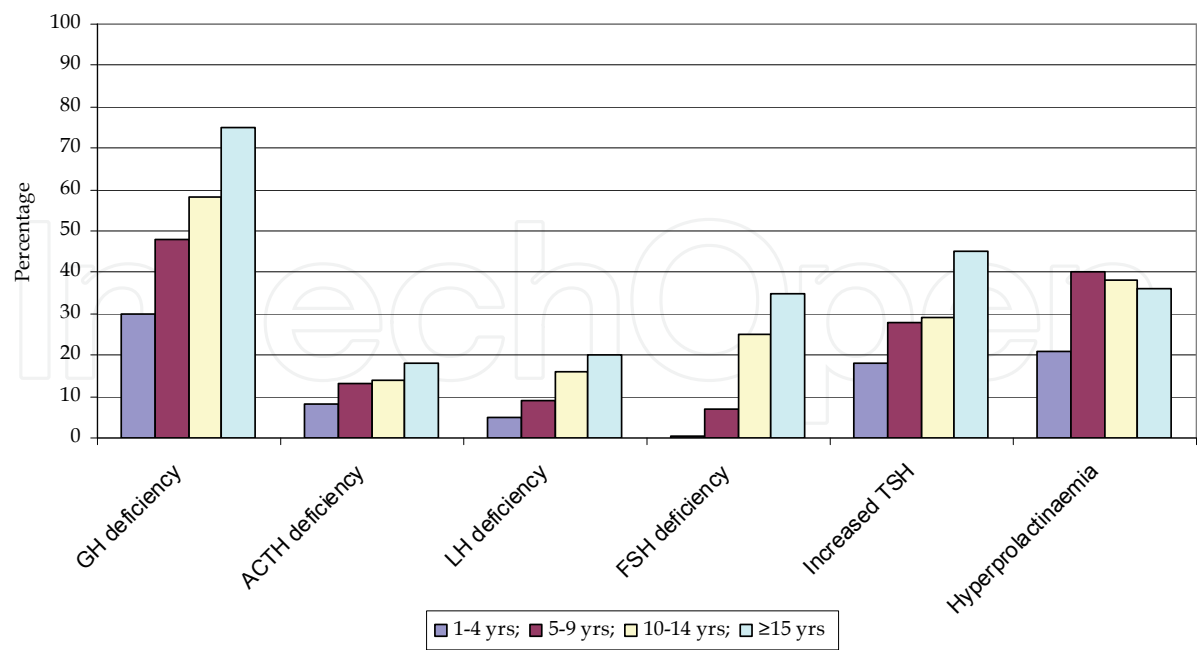


Fig. 2. Percentages of 166 patients with abnormal hormonal levels according to years after radiotherapy for NPC. Adapted from Samaan et al 1987 – Table II, with permission.

the other hand, is characterized by hypothalamic pattern of responses (delayed responses) to LHRH and TRH tests. A robust sign for hypothalamic damage is the occurrence of hyperprolactinaemia due to a reduction in hypothalamic release of the inhibitory neurotransmitter, dopamine. These abnormalities in hypothalamic functions have been clearly described in those intensively irradiated for nasopharyngeal carcinoma (Chen et al., 1989; Lam et al., 1991; Samaan et al., 1987) and skull base tumours (Pai et al., 2001) but much less frequently in those treated for other brain tumours or leukaemia with less intensive radiation schedules (Constine et al., 1993; Rose et al., 1999).

## **2.2 Growth Hormone (GH) deficiency**

### **2.2.1 Epidemiology and pathophysiology**

GH deficiency is the earliest manifestation of neuro-endocrine injury following cranial irradiation. With intensive irradiation used for NPC, the cumulative frequency of GH deficiency is well above 60% after 5 years (Lam et al., 1991). Higher incidence of severe GH deficiency is seen with longer follow up periods reaching well above 80% (Samaan et al., 1987). Given the higher radiosensitivity of the GH axis, GH deficiency is almost always present if deficiencies of one or more of the other anterior pituitary hormones are confirmed. Studies of stimulated GH secretion in children treated for brain tumours indicate that almost all children treated with doses in excess of 35 Gy will have blunted GH secretion within 2-5 years of treatment (Clayton & Shalet, 1991). With the more intensive radiation used for NPC, all children treated for this condition will undoubtedly manifest features of severe GH deficiency soon after irradiation.

Apart from the higher radiosensitivity of the GH axis in children, the higher frequency of severe GH deficiency in children may be explained by the much higher threshold of peak GH response to stimulation used to diagnose GH deficiency in this age group. Children who have been categorised as having severe GH deficiency may in fact be categorised as having normal GH status when retested in adult life. This apparent discrepancy is not related to recovery of the GH axis, but can be attributed to the use of more strict thresholds for the diagnosis of GH deficiency in adults (Shalet et al., 1998).

GH is secreted in a pulsatile manner with a diurnal variation. The latter is characterised by nocturnal increase in GH secretion. This complex pattern of secretion is under hypothalamic control. Recent pathophysiological studies by the author et al of stimulated and spontaneous GH secretion in a cohort of adult cancer survivors irradiated for brain tumours with doses of less than 50 Gy, suggested that hypothalamic regulation of GH secretion in patients with severe GH deficiency is maintained with preserved pulsatility and diurnal variation (Darzy et al., 2005, 2006). The reduction in GH levels appears to be related to a predominant quantitative damage to the pituitary somatotrophs leading to reduced GH pulse amplitude but not frequency. Another study by the author et al (Darzy et al., 2007) has suggested the presence of a compensatory increase in hypothalamic GHRH release to maintain a normal spontaneous GH secretion in patients with reduced pituitary somatotrophs reserve indicated by reduced peak GH responses to direct stimulation with the most potent GHRH and Arginine stimulation test. There has also been a suggestion for the presence of 'compensated GH deficiency' in some patients who would otherwise have been diagnosed with GH deficiency due to impaired peak GH responses to insulin-induced



hypoglycaemia (Darzy et al., 2009). It is unknown if the dynamics of GH secretion in patients with GH deficiency following intensive irradiation for NPC, with high probability of hypothalamic damage, are similar to what has been described by the author in patients with history of less intensive irradiation.

### 2.2.2 Diagnosis

Given the pulsatile nature of GH secretion, a single estimation of GH level is meaningless for the biochemical confirmation of a suspected GH deficiency. Physiological tests of GH secretion, such as 24-hour or nocturnal GH profiling are rarely used in routine clinical practice. In current clinical practice, the diagnosis of GH deficiency relies on demonstrating a subnormal peak GH response to pharmacological tests that provoke GH release due to direct stimulation of the pituitary somatotrophs or indirectly through stimulation of the hypothalamus. Various dynamic tests are used in clinical practice; the choice is largely influenced by the experience of the endocrine centre and to some extent by patient's requirement. The insulin tolerance test (ITT) remains the gold standard, especially in the irradiated patients (Lissett et al., 2001), unless contraindicated due to epilepsy or heart disease. Other tests that are commonly used in clinical practice include Glucagon stimulation test, Arginine stimulation test (AST), L-Dopa test, GHRH test and the GHRH+AST.

The cut-off peak GH threshold used to define GH status following various stimuli is arbitrarily defined (Hoffman et al., 1994; Shalet et al., 1998). In children, the peak GH response to the ITT or equipotent tests (Glucagon, AST, L-Dopa or GHRH) below which a child is considered to be suffering from GH deficiency has been gradually increased and currently most GH therapy would be considered, in the appropriate clinical context, if that child failed to achieve a peak GH response above 20 mU/L (7 µg/L) (Shalet et al., 1998). In adults, however, severe GH deficiency for which GH replacement therapy may be considered is defined as a peak response to ITT or equipotent tests of less than 9 mU/L (3 µg/L) (Growth Hormone Research Society, 1998) and less than 9 µg/L for the GHRH+AST (Aimaretti et al., 1998).

Additional support for diagnosing GH deficiency may be obtained from measuring GH-dependent markers including insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3). It is to be noted, however, that age and gender-corrected IGF-I and/or IGFBP-3 levels are frequently normal in patients with documented radiation-induced GH deficiency defined by physiological and/or pharmacological tests (Achermann et al., 1998; Cicognani et al., 1999; Tillmann et al., 1998). Thus, it had been thought that neither of these markers can be used as a reliable index of the development of radiation-induced GH deficiency. In general, a reduction in age- and gender-corrected IGF-I levels by 2 standard deviation (SD) is supportive of a diagnosis of GH deficiency providing other causes that reduce IGF-I production have been excluded, such as malnutrition, hypothyroidism, renal failure, liver disease, or diabetes mellitus (Shalet et al., 1998). In patients with panhypopituitarism, the diagnosis of GH deficiency is almost certain especially if IGF-I levels are significantly reduced and biochemical confirmation can almost always be achieved accurately with a single test.

In addition to biochemical tests, auxological measurements of the irradiated child at regular intervals may provide invaluable information about the GH status. Growth in children is a sensitive marker of GH status. Thus, in the absence of other aetiologies for growth retardation, the presence of significant growth deviation over a one year period, that is, growth velocity below the 25th centile or a drop in height of  $\geq 1$  standard deviation (SD) is highly suggestive of clinically significant GH deficiency, particularly in the appropriate clinical context, i.e. previous irradiation.

2.2.3 Clinical impact and treatment

GH deficiency is an important cause for impaired linear growth in irradiated children cured from cancer. Ample evidence from studies in brain tumour survivors suggests that GH therapy in those patients prevent further height loss and maintain their initial height centile to adulthood (Clayton et al., 1988; Sulmont et al., 1990) while those who do not receive treatment show further deterioration in their height centiles with a tendency for extreme short stature (Brauner et al., 1989; Clarson & Del Maestro, 1999). In addition, those patients may also need GH replacement therapy in the transition to adulthood to maximize bone density and prevent osteoporosis, which is a frequent finding in the irradiated cancer survivors (Brennan et al., 2005; Murray et al., 1999; Shalet & Rosenfeld, 1998).

In adults, GH deficiency may be associated with symptoms and signs of the well described adult GH deficiency syndrome (Table 1), in particular impaired quality of life (QoL) (de Boer et al., 1995).

GH replacement therapy in the irradiated adult cancer survivors may improve QoL, as in those with GH deficiency due to pituitary tumours (Murray et al., 2002). Thus, it is important that a robust diagnosis of radiation-induced GH deficiency is made so that appropriate GH replacement therapy can be introduced at the right time. Despite the numerous and proven benefits of GH replacement therapy in adults (Table 2), this is currently only recommended to primarily improve QoL. It is given on a trial basis with

1- Increased fat mass (especially truncal) and increased waist/hip ratio
2- Reduced lean body mass (reduced muscle bulk and strength)
3- Osteopenia and Osteoporosis
4- Adverse lipid profile (increased LDL and reduced HDL)
5- Glucose intolerance and insulin resistance
6- Impaired fibrinolysis and nitric oxide generation
7- Altered cardiac function and structure
8- Reduced exercise capacity and muscle strength
9- Reduced quality of life (QoL)
A- Reduced vitality
B- Reduced energy
C- Depressed mood
D-Increased anxiety
E- Increased social isolation
F- Impaired emotional and self-control

Table 1. Features of the adult growth hormone deficiency syndrome.



gradual dose titration to achieve an IGF-I level in the upper quartile of the normal range (Bengtsson et al., 2000). The treatment is administered as a daily subcutaneous injection. Treatment is withdrawn if there is no improvement in QoL after 9 months of treatment. GH therapy for severe osteoporosis, but not QoL issues, remains controversial.

2.2.4 Timing of testing

Testing for GH deficiency should be initiated at the time when GH therapy is considered safe. It is generally agreed that GH therapy should be avoided in the first 2-3 years after completion of cancer treatment, when the chance of cancer recurrence is greatest. GH therapy offered within this time period may be associated with a number of tumour recurrences and deaths that many families and doctors would associate with GH therapy despite a lack of proof of a causal relationship between GH therapy and tumour recurrence (Shalet et al., 1997; Sklar, 2004; Wilton, 1994).

Given the very high chance of developing severe GH deficiency 2-3 years after intensive radiotherapy in children, offering GH therapy without recourse to GH tests or evidence of impaired growth is an acceptable approach in certain centres. Alternatively, others would consider GH therapy when GH deficiency is established biochemically irrespective of growth rate. These approaches assume, given the epidemiological evidence, that it is highly likely that growth will soon decline in those patients or that an “apparently” normal growth rate is perhaps subnormal. A more selective approach, however, is still adopted by some endocrinologists who would insist on biochemical evidence of GH deficiency and a subnormal growth rate before initiating GH treatment. If GH status appears to be normal and the growth rate is appropriate for pubertal status, then growth is observed closely and the GH stimulation tests are repeated annually.

Testing in adults is only indicated if GH replacement therapy is to be considered in those who manifest symptoms and signs suggestive of severe GH deficiency (de Boeret al., 1995) (Table 1). A normal test 15 years after radiotherapy usually eliminates the need for further annual testing, as further decline in GH secretion is unlikely to occur after that time from radiotherapy.

Radiation-induced GH deficiency is irreversible. However, retesting in adulthood of those who were diagnosed with GH deficiency in childhood is mandatory before adult GH therapy is initiated or continued to address quality of life (QoL) issues. This is because the diagnostic threshold to treat GH deficiency is much lower in adults compared with children.

1- Improved psychological well-being and quality of life
2- Normalisation of body composition (reduced fat mass and increased lean body mass)
3- Increased bone mineral content
4- Increased ECF volume and renal function
5- Improved cardiac function
6- Improved exercise capacity
7- May reduce mortality in hypopituitary patients

Table 2. Benefits of growth hormone replacement therapy in adults.

### 2.3 Gonadotrophin deficiency

The gonadotrophin axis is the second most vulnerable to radiation damage. Gonadotrophin deficiency is frequently seen after intensive h-p axis irradiation (Chen et al., 1989; Constine et al., 1993; Lam et al., 1991; Rappaport et al., 1982; Samaan et al., 1987).

Gonadotrophin deficiency varies from subtle (subclinical) abnormalities in secretion detected only by GnRH testing to severe impairment associated with diminished circulating sex hormone levels. Although abnormalities in LH/FSH secretion can be demonstrated on dynamic testing, sometimes as early as one month following high dose irradiation (Chen et al., 1989), clinically-significant gonadotrophin deficiency is usually a late complication with a cumulative incidence in excess of 20% after long term follow up whether radiation was administered in childhood or adult life (Agha et al., 2005; Constine et al., 1993; Lam et al., 1991; Rappaport et al., 1982; Samaan et al., 1987). For example, Lam et al (Lam et al., 1991) reported a cumulative incidence of 30.7% 5 years after radiation treatment of NPC, while Samaan et al (Samaan et al., 1987) reported LH and FSH deficiency in 20% and 35% of NCP patients 1-4 years and more than 15 years after radiotherapy, respectively.

The diagnosis of gonadotrophin deficiency is confirmed by normal or low normal basal LH/FSH with diminished circulating sex hormone concentrations. In children, gonadotrophin deficiency may retard pubertal development and linear growth, especially in the context of GH deficiency, which almost always occurs following radiation doses that causes gonadotrophin deficiency. Those children will typically have a delayed bone age as assessed by a wrist radiograph. Treatment with sex steroids is needed to induce and support development of secondary sex characteristics as well as linear growth. It is extremely important that GH deficiency is recognised and treated for some time before introducing sex steroids to maximise the chances of attaining normal height.

In adults, secondary hypogonadism is associated with sexual dysfunction and reduced fertility. In the long term sex steroid deficiency may have adverse impact on metabolic, cardiovascular, muscular, and skeletal health and quality of life (QoL). Patients should be tested at regular intervals and whenever the diagnosis is suspected clinically. Women may present with oligomenorrhoea, amenorrhoea, sweating, and/or hot flushes. Men may complain from reduced libido, erectile dysfunction, reduced shaving frequency, fatigue and tiredness, mood changes and weight increase with central adiposity. Treatment with sex steroid replacement therapy improves QoL and prevent decline in physical and mental health. Gonadotrophin therapy is needed to restore fertility, unless gonadal damage from chemotherapy coexists.

GnRH testing may help to differentiate between hypothalamic and pituitary cause for gonadotrophin deficiency. A delayed peak gonadotrophin response and/or a delayed decline indicate hypothalamic damage; a blunted response indicates pituitary damage or secondary pituitary atrophy; a mixed pattern of responses indicates possible damage at both sites. Repeated intermittent infusion of GnRH may restore pituitary responsiveness and therefore differentiate between primary and secondary pituitary atrophy (Yoshimoto et al., 1975) and with prolonged treatment there is the potential for restoring gonadal function and fertility (Hall et al., 1994).

## 2.4 ACTH deficiency

The hypothalamic-pituitary-adrenal axis appears to be the most radioresistant in patients irradiated for non-pituitary disorders. Clinically apparent ACTH deficiency occurs in only about 3% of patients receiving a total radiation dose to the h-p axis of 40-50 Gy (Constine et al., 1993; Livesey et al., 1990). In contrast, the frequency of ACTH deficiency in patients treated with intensive irradiation for NPC is significantly higher. Samman et al (Samaan et al., 1987) reported a frequency of 4% in the first 4 years after irradiation and a cumulative frequency of 20% after 15 years, while Lam et al (Lam et al., 1991) reported a cumulative frequency of 30.7% after 5 years. Differences in radiation schedules and diagnostic criteria may explain the higher frequency in the latter study (Lam et al., 1991). In most reported cases, however, ACTH deficiency was partial and only a few patients needed regular hydrocortisone replacement because of symptoms of hypocortisolism (Lam et al., 1991; Samaan et al., 1987; Samaan et al., 1982).

From a clinical perspective, significant as opposed to subtle abnormalities in ACTH secretion, are unlikely to be missed by the ITT, which remains the “gold standard”. If the ITT is contraindicated, alternative tests like Glucagon and Synacthen may be considered. Measurements of 9 am cortisol may be adequate; a level in excess of 300 nmol/l almost always excludes significant ACTH deficiency. However, during periods of acute stress or acute illness, a level in excess of 500 nmol/l is required to confirm normality of the ACTH-adrenal axis. Patients with lower levels or those who are symptomatic should be considered for a stimulation test. As ACTH deficiency is a slowly evolving abnormality, it is very unusual to have a normal synacthen test in the context of a clinically significant ACTH deficiency that normally results in secondary adrenal atrophy.

It is to be noted that increased oestrogen levels due to HRT, use of contraceptive pill (OCP) or pregnancy may raise cortisol binding globulin (CBG) resulting in spurious elevation of circulating total cortisol levels by as much as 3 folds or more. Under these circumstances, an apparently normal random cortisol level may occur in the presence of a significant cortisol deficiency. Any assessment of cortisol levels should only be done after withdrawing any oestrogen containing medications for at least 4 weeks. If the patient was on the oral contraceptive pill (OCP) appropriate advice about mechanical contraception should be provided. If the patient is not willing to stop oestrogen replacement therapy or if pregnant, a stimulation test may be needed. The normality of the ACTH-adrenal axis is then determined by a normal cortisol increment rather than by the normality of the absolute basal or stimulated cortisol levels.

Adrenal dysfunction with reduction in spontaneous and/or stimulated cortisol secretion is an important diagnosis to make. Missing a diagnosis of this nature may put patients at risk of acute adrenal crisis during periods of acute stress. Although regular hydrocortisone replacement therapy may not be necessary in asymptomatic patients with partial ACTH deficiency, oral or intravenous hydrocortisone replacement therapy may become necessary during situations that can lead to acute adrenal crisis due to failure of the ACTH-adrenal axis to meet the increased demands for cortisol. Such patients should be properly informed about the emergency use of hydrocortisone during severe stress, acute illness, surgery, and trauma. Patients should also be advised to have a steroid medi-alert bracelet for emergency situations.

Patients with clinically significant ACTH deficiency may experience symptoms of adrenal insufficiency including poor appetite, nausea, vomiting, tiredness, easy fatigability, muscle weakness, and breathlessness on exertion. Weight loss may not occur due to coexisting GH deficiency and/or hypothyroidism, which cause central obesity. Regular replacement therapy is strongly recommended in those patients.

## 2.5 TSH deficiency

Like the ACTH axis, the hypothalamic-pituitary-thyroid axis appears to be the least vulnerable to radiation damage and the latter is highly dose-dependent (Constine et al., 1993; Lam et al., 1991; Littley et al., 1989a). With radiation doses of less than 50 Gy, the frequency of TSH deficiency remains as low as 3-6%, such as that found in survivors of non-pituitary brain tumours (Livesey et al., 1990; Oberfield et al., 1992). Patients irradiated during adulthood for non-pituitary brain tumours were reported to have 9% rate of secondary hypothyroidism (Agha et al., 2005). A higher incidence of overt secondary hypothyroidism is noted in patients with pituitary tumours (Littley et al., 1989a), but more frequently following intensive irradiation schedules utilizing doses in excess of 50 Gy, typically used for head and neck tumours including NPC (Chen et al., 1989; Constine et al., 1993; Lam et al., 1991; Pai et al., 2001; Samaan et al., 1987). For example Lam et al (Lam et al., 1991) reported a cumulative incidence of secondary hypothyroidism of 14.9% after 5 years of follow up. The exact incidence of TSH deficiency may be under-estimated in NPC patients due to the high frequency of co-existing primary thyroid dysfunction causing TSH elevation.

Annual testing of thyroid function is indicated in patients irradiated for NPC who are particularly at much greater risk of primary hypothyroidism due to radiation-induced damage of the thyroid gland. The diagnosis of frank central hypothyroidism is straightforward - subnormal T4 level with normal or low basal TSH concentration. Given the wide range of normal free T4 levels, a significant decline in free T4 levels over time with normal or low normal TSH levels may signify a diagnosis of evolving central hypothyroidism or a mixed (primary and secondary) hypothyroidism even before free T4 levels drop below the lower normal limit. This should be highly suspected in the presence of gonadotrophin and/or ACTH deficiency or if there is history of thyroidal irradiation and it may warrant a therapeutic trial with thyroxine in the presence of a supportive clinical picture.

Thyroxine replacement therapy may precipitate symptomatic acute adrenal insufficiency in an otherwise asymptomatic individual with unrecognised ACTH deficiency. It is mandatory that reduced cortisol production be ruled out with certainty before starting thyroxine therapy. If cortisol deficiency coexists, it should be treated first before intruding thyroxine therapy. It is also important to continue to assess the ACTH-adrenal axis at regular intervals after commencing thyroxine replacement therapy.

With the difficulty in diagnosing evolving central hypothyroidism by a single test, it has been claimed that the presence of a hypothalamic TSH response to a TRH test and/or diminished nocturnal TSH surge despite a normal free T4 level may imply a diagnosis of so-called "hidden" central hypothyroidism in a substantial proportion of irradiated children (Rose et al., 1999). In a recent study by the author et al (Darzy & Shalet, 2005), however, it was demonstrated that, like in some normal individuals, the loss of nocturnal TSH surge



seen in about 20% of euthyroid adult cancer survivors did not reflect a genuine loss of diurnal rhythm, but simply occurred as a result of a physiological shift in the timing of the peak TSH (acrophase) and/or the nadir TSH levels potentially leading to an erroneous diagnosis of “hidden” central hypothyroidism. Therefore, serial thyroid testing to demonstrate a decline in T4 levels provides the only means for diagnosing “hidden” central hypothyroidism.

## 2.6 Hyperprolactinaemia

Radiation-induced hyperprolactinaemia is mostly seen following intensive irradiation due to hypothalamic damage leading to a reduction in the inhibitory neurotransmitter dopamine. It has been described in both sexes and all age groups but is most frequently encountered in the adult female with radiation doses in excess of 40 Gy. In these patients, a mild to modest elevation in prolactin level is noticed in 20-50% (Agha et al., 2005; Constone et al., 1993; Lam et al., 1991; Littley et al., 1989a; Samaan et al., 1987) compared with less than 5% in children (Rappaport et al., 1982) and after low radiation doses (Littley et al., 1991). A much higher incidence is seen following intensive irradiation; Chen et al (Chen et al., 1989) reported hyperpractinaemia in 21% and 36% in the first 4 years and after 15 years of radiotherapy in NCP, respectively.

Radiation-induced hyperprolactinaemia is not clinically significant in the vast majority of patients. Occasionally, it may be of sufficient severity to impair gonadotrophin secretion and cause pubertal delay or arrest in children, decreased libido and impotence in adult males and galactorrhoea and/or ovarian dysfunction in women (Samaan et al., 1982). A gradual decline in the elevated prolactin level may occur with time and can normalize in some patients. This may reflect time-dependent slowly evolving direct radiation-induced damage to the pituitary lactotroph (Littley et al., 1989b).

Radiation-induced hyperprolactinaemia responds very well to treatment with dopamine agonists. Galactorrhoea resolves soon after normalising prolactin levels. However, treatment with dopamine agonists will only restore gonadal function and fertility if there is no co-existing gonadotrophin deficiency or primary chemotherapy-induced gonadal damage.

## 3. Radiation-induced primary thyroid dysfunction

Primary hypothyroidism is the most common clinical consequence of radiotherapy to the cervical area. It is well described in patients treated for Hodgkin’s disease with a cumulative incidence of 44% after 25 years of radiotherapy (Hancock et al., 1991). The intensity of the damage, and hence, the degree of thyroid dysfunction is both dose- and time-dependent (Sklar et al., 2000). Primary hypothyroidism has been reported with fractionated radiotherapy with doses exceeding 25 Gy (Shalet et al., 1977). The probability of developing primary thyroid failure is significantly increased beyond 45 Gy (Bhandare et al., 2007). Chemotherapy has not been shown to influence the development of thyroid dysfunction following standard radiation therapy for head and neck cancers (Miller & Agrawal, 2009).

The pathophysiological mechanisms underlying radiation-induced thyroid dysfunction remain controversial. Various mechanisms have been proposed including radiation-induced autoimmune thyroiditis, direct radiation-induced damage to the follicular epithelium, direct

microvascular and macrovascular damage resulting in thyroid tissue hypoxemia and nutrient-poor environment leading to reduced synthetic and secretory capacity, and radiation-induced fibrosis that may prevent compensatory hypertrophy of the gland (Miller & Agrawal, 2009). The development of thyroid antibodies after radiotherapy may predict a higher chance of thyroid dysfunction in the long-term.

Subtle thyroid dysfunction occurs soon after radiotherapy for NPC; Chen et al (Chen et al., 1989) have demonstrated increased peak TSH responses to TRH stimulation a month after radiotherapy and more so after 15-18 months of radiotherapy. More severe degrees of thyroid dysfunction with increased TSH and reduced free T4 tend to occur in the long term. However, hypothyroidism may occasionally develop as early as 6 weeks after completion of high dose radiotherapy to the neck.

A cumulative incidence of increased TSH of 18% and 45% was reported in 166 patients treated for NPC in the first 4 years and after 15 years of follow up, respectively (Samaan et al., 1987). In a prospective study of 408 patients who had received radiation therapy for NPC; the estimated incidences for clinical hypothyroidism were 5.3%, 9.0%, and 19.1% and for sub-clinical hypothyroidism were 9.7%, 15.7%, and 20.5% at 3, 5 and 10 years after radiotherapy, respectively (Wu et al., 2010). This study has also showed that clinical hypothyroidism occurred more frequently in younger patients, female sex and following conformal radiotherapy. Some reports have also suggested a higher incidence of radiation-induced hypothyroidism in the younger age group treated for Hodgkin's disease (Shalet et al., 1977) or for NPC (Zubizarreta et al., 2000), while other reports did not (Daoud et al., 2003; Kupeli et al., 2006). These rates of radiation-induced hypothyroidism are significantly higher than the reported rates of 0.3-1.3% in the general population (Wu et al., 2010). Much higher rates of hypothyroidism are seen in other head and neck tumours that involved thyroid surgery in addition to radiotherapy (Wu et al., 2010).

The diagnosis of primary hypothyroidism is straight forward. Frank (clinical) hypothyroidism is associated with increased TSH and subnormal free T4. Sub-clinical cases are characterised by increased TSH but apparently normal free T4. The presence of radiation-induced hypothalamic-pituitary damage with TSH deficiency may compound the biochemical picture and interpretation of the thyroid functions tests. Significant reduction in free T4 levels, albeit in the normal range, may be seen in the presence of normal or slightly elevated TSH levels. Under these circumstances a trend showing a progressive decline in free T4 levels despite a stable/mild increase in TSH levels following radiotherapy supports the diagnosis of central hypothyroidism or a combined primary and secondary hypothyroidism that may warrant a trial of thyroxine replacement therapy.

It is recommended that all patients have a thyroid function test at baseline and every 6-12 months after radiotherapy. Symptoms and signs of hypothyroidism should be explored during any consultation. The symptoms of overt hypothyroidism include weight gain or difficulty losing weight, intolerance to cold, dry skin, hair loss, constipation, menorrhagia or intermenstrual spotting, decrease physical activity, lethargy, easy fatigability, muscle cramps, and slow mentation. The signs include periorbital oedema, loss of eyebrows, cool and dry skin, a prolonged relaxation phase of deep tendon reflexes, and pleural or pericardial effusions. If the biochemical diagnosis is uncertain, a trial of thyroxine replacement therapy in those with "sub-clinical" hypothyroidism with "normal" free T4 levels is worth considering with a proper assessment of the response.



In contrast to hypothyroidism, the frequency of hyperthyroidism due to Garves' disease is slightly increased post-irradiation (Jereczek-Fossa et al., 2004).

#### **4. Radiation-induced thyroid nodules and tumours**

The development of thyroid nodules and benign and malignant neoplasms is well described in patients who received neck irradiation for Hodgkin's lymphoma (Oeffinger et al., 2003) or as part of cranio-spinal irradiation for brain tumours (Shalet et al., 1977). There is no literature on this complication following treatment of NPC.

A significantly increased risk is seen in children irradiated before the age of 10 years. Other risk factors include female sex, longer duration of follow up and increased radiation dose above 2 Gy with no reduction in risk with high radiation doses reaching 60 Gy. Most of these thyroid nodules are benign in nature and may regress (Jereczek-Fossa et al., 2004). The risk of nodules being malignant is significantly higher if irradiation was administered before age 16 years and the tumourigenic effects of radiation in this age group can last up to 40 years post treatment (Schneider et al., 1993).

The frequency of diagnosed thyroid nodules after irradiation depends on the diagnostic method used. Clinical examination is usually not robust enough to detect small nodules less than 2cm in size. High-resolution thyroid ultrasound has increased the detection frequency (Mihailescu et al., 2005). Thyroid ultrasonography also helps to identify suspicious nodules that need a diagnostic fine needle aspiration (FNA). Routine surveillance ultrasonography of the thyroid remains a controversial issue, as it may increase anxiety and unnecessary diagnostic interventions. However, patients at high risk of radiation-induced thyroid cancer should undergo regular surveillance ultrasonography. FNA should be performed for suspicious nodules by virtue of size, rapidity of growth and/or ultrasonographic appearance. A diagnostic partial thyroidectomy may also be needed if the FNA was inconclusive.

#### **5. Chemotherapy-induced gonadal damage**

The gonads are extremely sensitive to chemotherapy. Gonadotoxicity with resulting gonadal failure is a significant complication, which is seen more frequently than before due to increased use of chemotherapy in NPC, in particular Cisplatin, which is highly gonadotoxic.

##### **5.1 Chemotherapy-induced ovarian damage**

Chemotherapy-induced ovarian damage depends on the type and the total dose of the drugs used. The chemosensitivity of the ovary is age-dependent with progressively smaller doses being required to produce ovarian failure with increasing age (Rivkees & Crawford, 1988). Chemotherapeutic agents known to be gonadotoxic include alkylating agents, in particular Cyclophosphamide, Vinca-alkaloids, Antimetabolites, Platinum agents (Cisplatin) and others such as Procarbazine.

Cisplatin is the most commonly used agent in the treatment of NPC. The pathophysiological mechanisms underlying chemotherapy-induced ovarian damage are not

fully understood. They are thought to be related to the cytotoxic effects of the drugs on ovarian follicles leading to impairment of follicular maturation and/or depletion of primordial follicles.

Chemotherapy-induced ovarian damage is unlikely to occur in the pre-pubertal patients. However, it is quite frequent in women with a frequency reaching 50% in those who received Alkylating agents. Acute ovarian failure may occur shortly after completion of chemotherapy. Recovery of acute ovarian failure is variable and can occur after many months or even years of amenorrhoea. Patients who retain their ovarian function after completion of chemotherapy and those who recover from acute ovarian failure are still at risk of early or premature ovarian failure later in life (Howell & Shalet, 1998).

Depending on severity, chemotherapy-induced ovarian damage can lead to delayed, arrested or absent pubertal development (in children), oligomenorrhoea, amenorrhoea, infertility, or sub-fertility. Oestrogen deficiency symptoms such as hot flushes, sweating, sexual dysfunction, and psychosomatic complaints are common especially with acute ovarian failure. These symptoms can have very negative impact on quality of life and physical well-being. In the long-term early ovarian failure may lead to accelerated decline in bone density and osteoporosis, increased cholesterol levels and possible increased risk of cardiovascular disease. Adequate oestrogen replacement therapy is recommended to relieve symptoms and preserve bone density, especially in younger people providing there are no contra-indications for their use. The decision to use HRT and its duration should be individualised and agreed with the patient taking into account the benefits and the long-term risks of HRT.

Biochemically, ovarian damage is characterised by reduced oestrogen levels and increased gonadotrophin levels and/or impaired ovulation tests. The compensatory increase in FSH/LH levels may be attenuated or completely absent if radiation-induced gonadotrophin deficiency coexists.

Fertility preservation in young women, if resources allow, should be considered and offered to certain patients depending on their age, presence of a partner, desire for fertility, psychosocial issues, and the extent of the disease and prognosis. Methods to preserve fertility in women include freezing (embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation) and ovarian suppression with GnRH analogues or antagonists. Unfortunately, fertility preservation techniques are not widely available and each method has its own advantages and disadvantages with no guaranteed outcome (Howell & Shalet, 2002).

## 5.2 Chemotherapy-induced testicular damage

Temporary or permanent chemotherapy-induced testicular damage occurs at all ages of life (Howell & Shalet, 2001, 2005). Unlike in females, children seem to be more susceptible to the damaging effects of cytotoxic agents. Although all chemotherapeutic drugs may have some effects on fertility, some are known to be more gonadotoxic than others. Alkylating agents are the most gonadotoxic; others include Cisplatin, Cytarabine, Dacarbazine and Procarbazine. The germinal epithelium in the seminiferous tubules is more chemo-sensitive than Leydig cells. Germinal epithelium damage following chemotherapy can be seen in the presence of normal Leydig cell function. Depending on the type and number of agents

administered and the total dose, damage to the germinal epithelium and the supporting Sertoli cells, with consequent oligo- or azoospermia, occurs in 20-90% of patients following chemotherapy. Recovery of spermatogenesis is not unusual and can be seen several years after chemotherapy (Howell & Shalet, 2005). In patients treated for testicular cancer, for example, variable degrees of recovery of spermatogenesis are seen in 50-80% after 2 to 5 years following completion of cisplatin-based chemotherapy (Howell & Shalet, 2005). However, patients who have fully preserved or recovered spermatogenesis still have reduced sperm count compared with healthy men. Damage to the germinal epithelium causes gradual atrophy of the testes with reduced volume, reduced inhibin B and increased FSH secretion.

Although less vulnerable to the cytotoxic effects of chemotherapy than the germinal epithelium, Leydig cell dysfunction following chemotherapy is well described. It is often fully compensated with normal testosterone levels and significantly increased LH levels (Howell & Shalet, 2001). The effects of chemotherapy on the production of testosterone from Leydig cells are only seen at much higher doses. The doses required to cause Leydig cell failure will invariably have resulted in damage to the germinal epithelium. However, subtle degrees of Leydig cell dysfunction may be seen in the presence of normal spermatogenesis (Howell & Shalet, 2001). Co-existing radiation-induced gonadotrophin deficiency may impair the extent of compensation and result in combined primary and secondary hypogonadism.

The impact of mild/subclinical Leydig cell insufficiency is unclear (Howell et al., 1999). However, the manifestations of severe degrees of Leydig cell dysfunction depend upon the age of the patient. Loss of Leydig cell function before the onset of, or during puberty will be associated with failure to enter puberty spontaneously or arrest of pubertal development. Leydig cell failure following the development of normal secondary sexual characteristics manifests clinically with reduced libido, erectile dysfunction, fatigue and mood changes. In the long-term, Leydig cell failure may adversely affect skeletal, muscular, cardiovascular, and metabolic health as well as cognitive functions (Bhasin et al., 2010). If not contraindicated, testosterone replacement therapy is recommended for symptomatic men with classical androgen deficiency aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density. Clinical monitoring of testosterone therapy at regular intervals to assess response, compliance and adverse effects is important. Assessment of bone density every 1-2 years in osteoporotic men and annual monitoring of the haematocrit and the PSA (in men 40 yr of age or older) are also important particularly in the long-term (Bhasin et al., 2010).

With regard to fertility preservation, cryopreservation of spermatozoa before sterilizing chemotherapy (sperm banking) in the sexually mature male is currently the only established clinical option. In men with spermatogenic arrest, sperm extraction for intracytoplasmic sperm injection (ICSI) is a potentially successful approach. Other fertility preservation techniques such as cryopreservation of testicular tissues, germ cell transplantation, testis tissue xenografting and hormonal manipulation are largely experimental (Howell & Shalet, 2002).

## 6. Conclusions

Treatment of NPC with radiotherapy is associated with a high risk of radiation-induced hypothalamic-pituitary dysfunction. More than 80% of NPC survivors will have at least one

anterior pituitary hormone deficiency and hyperprolactinaemia is frequently seen in women. Irradiation of the thyroid is associated with a significant risk of primary hypothyroidism. In the long-term there is increased risk of thyroid nodules and thyroid cancer, especially in children. These abnormalities in the endocrine functions are progressive and irreversible and can result in significant morbidity and impaired quality of life. In addition, chemotherapy may cause transient or permanent direct gonadal damage and hypogonadism. Regular endocrine surveillance is mandatory to achieve early detection of these abnormalities and timely treatment.

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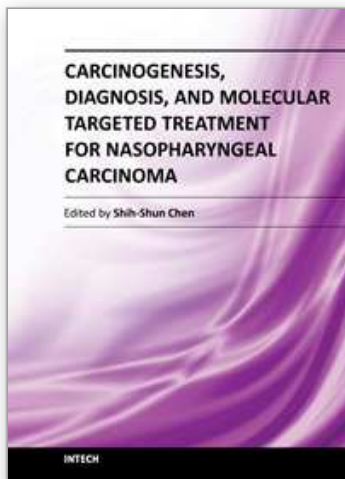
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## **Carcinogenesis, Diagnosis, and Molecular Targeted Treatment for Nasopharyngeal Carcinoma**

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