Radioiodine Therapy of Thyroid Cancer

3

Frederik A. Verburg

3.1 Introduction

3.1.1 Differentiated Thyroid Cancer

Although it concerns fewer than 1% of all cancer cases, and its incidence varies throughout the world [1], differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy [2]. This comprises the so-called papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). These tumours derive from the follicular thyrocytes and are referred to as "differentiated" thyroid cancer because the tumour cells retain some of normal thyrocytes' properties. Most importantly the ability to take up and store iodine and to respond to thyrotropin (thyroid-stimulating hormone, TSH) stimulation is retained, which allows for treatment and imaging using radioactive iodine analogues. DTC cases typically have a good prognosis, with long-term survival ranging from about 70% to more than 95%, depending on the extent of disease at the time of diagnosis [3]. Consequently, in >85% of DTC patients, life expectancy is unimpaired [4, 5].

3.1.1.1 Histology and Clinical Behaviour

PTC

The classical form of PTC is an unencapsulated tumour with papillary and follicular structures. It is characterized by overlapping cell nuclei that have a ground-glass appearance and longitudinal grooves, with invaginations of cytoplasm into the nuclei [6, 7]. PTC histologic variants among others include the encapsulated, follicular, tall-cell, columnar cell, clear-cell, diffuse sclerosing, solid or trabecular, and oxyphilic forms [2, 8]. PTCs are often multifocal, with many of the lesions of different clonal origin, i.e. arising independently [9]. PTC metastasis tends to be lymphogenic, before spreading to the lungs and bones.

FTC

FTC is characterized by follicular differentiation, without the nuclear changes seen in PTC [6, 7]. FTCs are encapsulated tumours, distinguishable from follicular adenomas by the presence of invasion of the capsule and/or vessels. According to the pattern of invasion, FTCs can be divided into two categories: minimally invasive and widely invasive. FTCs are less often multifocal than are PTCs. FTC tends to metastasize to the lungs, bone and liver; regional lymph node metastases are much less common than in PTC.

Hürthle cell carcinoma is a variety of FTC that consists of at least 75% oxyphilic cells [8]. An important characteristic of Hürthle cell carcinomas

F. A. Verburg (✉)
Department of Nuclear Medicine, University Hospital Marburg, Marburg, Germany
e-mail: verburg@med.uni-marburg.de

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is their reputedly poor or even absent iodine uptake, which renders this entity more difficult to treat.

3.1.1.2 DTC Treatment

In the treatment of DTC, multiple modalities are involved, each of which will be discussed separately.

Surgery

Surgery is the first and most important component of the primary treatment of DTC. In Europe, the Americas, and much of Australasia, (near) total thyroidectomy is usually performed in almost all patients. Only for papillary microcarcinoma hemithyroidectomy is deemed to suffice by most patients [9–17].

The most serious potential complications of thyroid surgery are hypoparathyroidism and recurrent laryngeal nerve damage [18, 19]. Identification and electronic monitoring of the recurrent laryngeal nerve can significantly reduce the rate of nerve damage [20]. The incidence and impact of complications can be reduced by performing the procedure in expert centres [19] as well as intensive post-operative monitoring, especially serum calcium levels should be monitored frequently in the immediate post-operative phase.

Thyroid Hormone Replacement Therapy

As by definition the production of endogenous thyroxine is discontinued by thyroidectomy procedure, DTC patients require thyroid hormone (levothyroxine, LT4) replacement therapy [21].

Differentiated thyroid cancer cells still react to TSH stimulation; for this reason LT4 in more advanced cases is usually administered in such doses that TSH levels fall to very low levels of <0.1 mU/L [22]. Especially for low-risk patients TSH suppression is not generally advocated [21].

Radioiodine (I-131) Therapy

A landmark study by Mazzaferri and Jhiang published in 1994 on a population of over 1500 patients followed for four decades or more clearly showed that both recurrence rates and death rates related to DTC were much lower in patients who received radioiodine treatment (RIT) after surgery than in those who did not receive I-131 [13]. In fact, now that I-131 therapy belongs to the standard treatment of DTC, life expectancy in patients without extensive neck or distant metastases is unimpaired [4].

I-131-NaI closely approaches the ideal oncologic drug. It is one of the earliest and longest used examples of selective targeted therapy [23]. It can be used both for imaging the drug distribution and for diagnostics and treatment. I-131-NaI is a very specific radiopharmaceutical for targeting cancer cells that have retained the normal thyrocytes' functional attributes as the body's main iodine reservoir and primary locus of expression of the sodium-iodide symporter (NIS) [24], making I-131 largely specific for the target cancer cell.

In clinical practice, post-operative, adjuvant I-131 therapy is primarily applied to destroy remaining occult small DTC foci, thus decreasing the long-term risk of recurrent disease [10, 13, 25–27]. Furthermore, by eliminating remaining normal thyroid tissue the specificity of serum thyroglobulin and diagnostic whole-body scans (dxWBS) as markers for persistent or recurrent DTC are improved [2, 26, 28]. Additionally, given the multiclonal nature of many DTC cases [9] by destroying healthy thyroid cells ablation may prevent neoplastic transformation from occurring again [29]. As an added bonus I-131 ablation allows sensitive post-ablation whole body scanning (rxWBS) for detecting previously unknown persistent locoregional disease or distant metastases [30, 31]. The latter does not however in itself constitute a goal or justification for I-131 ablation.

The effectiveness of I-131 ablation in the prevention of recurrent disease and DTC-related death has been shown sufficiently in multiple studies, especially in high-risk patients or in cases of non-radical surgery [13, 32, 33].

I-131 therapy has been used for treating DTC for over 75 years [23]. However, there still is no agreement on the activity of I-131 to use for which clinical situation, let alone on what parameters to use to determine the activity. As a reflec-

tion of this lack of evidence and procedural guidance physicians often still administer standard Iodine-131 dosages as fractions or multiples of "millicuries" although SI-units for the amount of radioactivity have been converted to "Becquerels" more than 30 years ago. Most often I-131 ablation or therapy is administered in the form of a standard activity. The simplest approach to individualize I-131 ablation using fixed activities is the empirical variation of this fixed activity according to stage and histological findings of the surgical specimen. Current guidelines are largely in consensus that the primary goal of initial I-131 therapy, adjuvant post-surgical thyroid remnant ablation, adjuvant treatment or therapy of remaining local or metastatic disease, should influence the therapeutic activity; to what extent is however subject of discussion [34–36]. In children, if no dosimetry is performed, the activity should furthermore be individualized according to body weight, in which the calculation is usually based on an activity per kg bodyweight given to a 70 kg adult [37–39].

3.2 rhTSH

High thyrotropin levels (above 30 mU/L) are usually recommended for I-131 therapy in order to induce sufficient I-131 uptake [34–36]. Such high TSH levels can be achieved either by thyroid hormone withdrawal (THW) for 3–4 weeks or by intramuscular injections of recombinant human TSH. Through avoidance of hypothyroidism, the use of rhTSH results in an unimpaired quality of life [40–42]. A further advantage of rhTSH is that it results in a lower radiation exposure to the remainder of the body, including the bone marrow [43], the reproductive system and the salivary glands [44, 45], thus at least in theory reducing the risk of complications. Over time, many studies have shown the equivalence of rhTSH to THW both for TSH-stimulated Tg testing with or without concurrent dxWBS [46] and for initial I-131 ablation of patients without distant metastases. Furthermore, rhTSH is likely cost-effective from several points of view [47, 48].

3.3 Salivary and Lacrimal Gland Damage (Sicca Syndrome)

One of the most frequent long-term complications of I-131 therapy concerns the salivary glands. As these physiologically take up I-131 as well, in some patients this causes a sufficient irradiation of the organ to cause permanent salivary gland dysfunction. This results in a permanent xerostomia (dry mouth) which severely impairs patients' quality of life.

Attempts have been made to protect the salivary glands during I-131 therapy by the intravenous administration of 500 mg/m^2 S-2-(3-aminopropylamino)-ethylphosphorothioic acid (amifostine) prior to therapy. In a double-blind trial the administration of amifostine leads to an unchanged salivary gland function compared to the pre-therapeutic situation, whereas patients who did not receive amifostine showed a highly significant reduction of the salivary gland function [49]. Treatment with a lower dose of 300 mg/m^2 in a later trial was shown not to be effective [50]. The concept of amifostine protection has not been explored further since, possibly due to potential side effects of the substance.

Traditionally it was thought that stimulation of the salivary glands using, e.g. lemon drops and/or chewing gum would lead to a lower radiation exposure to the salivary glands through an increased washout of I-131 in the excreted saliva. However, several recent studies have shown that this strategy, at least when applied immediately after I-131 administration, may on the contrary lead to an increased radiation exposure through an increase in blood flow to the salivary glands, resulting in an increased I-131 uptake [51]. There is some clinical evidence that delaying the start of stimulation to at least 24 h after the ingestion of I-131 may in fact lead to a lower rate of salivary gland dysfunction [52].

Less known than the damage to the salivary glands is the damage that may be caused to the lacrimal glands by I-131 therapy, the latter occurring with a much lower frequency. Nonetheless, the occurrence of both these phenomena is clearly less frequent subjectively than objectively, with objective xerostomia occurring objectively in the

great majority of patients even after only 3.7 GBq I-131 (38/46 patients; [53]) and in all patients after 14.8 GBq or more. However, only a minority of patients complained of this in the lower activity groups. Xerophthalmia was present in a lower percentage of patients (9/46 objectively, 7/46 subjectively after 3.7 GBq I-131 to 3/5 subjectively and 4/5 objectively in patients receiving 14.8 GBq I-131 or more; [53]).

3.4 Malignant Sequellae

Originally hailed in the popular press as a form of magic, it quite soon became evident that even this very specific, targeted drug is not without its long-term side effects and complications. First reports of acute myeloid leukaemia in DTC patients treated with I-131 were already published in the 1950s [54] by the group who first introduced I-131 for DTC. In the ensuing decades, many more scientific publications which examined the role of I-131 in inducing secondary malignancies emerged with differing results: some reports allege that I-131 does induce not only haematological but also possibly solid malignancies [55], whereas others could show that excess non-thyroid malignancy rates are observed in similar heights before as well as after I-131, making a causal relationship with I-131 unlikely [56].

Nonetheless, that exposure to radioactive iodine might cause an increase in the rate of secondary haematological (or other) malignancies is not implausible. I-131 will, after oral or i.v. application, first circulate systemically before being taken up in DTC cells. Well-perfused organs such as the bone marrow are therefore exposed to similar radiation absorbed doses as the blood itself—as was already shown in the 1960s [57]. As the red bone marrow is a highly proliferative tissue, it is also highly sensitive to any DNA-damaging agents or interventions (this is not just limited to radiation, but may also include cytotoxic chemotherapy), which may cause a short-term depression in complete blood cell counts (CBCs) [58, 59]. Furthermore, at least in theory, DNA damage to this highly proliferative tissue may in the long term contribute to the induction of malignant neoplasms.

Recently, new data were published which showed again that it is not unlikely that I-131 therapy of DTC may cause secondary haematological malignancies [60, 61]. Although these reports show a significant increase in the risk of such secondary malignancies, these studies can nonetheless also be regarded as evidence *in support of* radioiodine therapy in DTC. As was detailed in calculations by Piccardo et al. [62], the data presented by Molenaar et al. allow the calculation of the absolute excess risk of haematological malignancies in DTC patients treated with I-131. This risk approximately amounts to one case per ten million patient years [62]. Even assuming that all these cases will result in a fatality—which is hardly likely the case—I-131 may still compare favourably to not giving I-131, e.g. by missing the diagnosis of and thereby timely treatment of distant metastases when this treatment modality is omitted. In fact, this excess risk is so small as likely to be unnoticed in the individual physicians' life-long practice. So small in fact, that it may be less risky in terms of risk of mortality to perform I-131 than to make a patient drive to the attending physicians' office more often, than taking an aspirin [63], or many other environmental risks from daily life.

3.5 Haematological Complications

As detailed above, I-131 may affect the red bone marrow. Not only does this contribute to an elevated risk of secondary haematological malignancies but also to a risk of impairment of bone marrow function. Molinaro et al. detailed in 2009 that one year after I-131 ablation, white blood cell and platelet count was still significantly lower than at baseline, even though the difference was minor and not clinically relevant [58]. Long-term data were not reported by these authors. Verburg et al. reported on the effects of dosimetrically determined high activities of I-131 on blood cell counts and found that, although there was a marked but non-critical effect in the short

term, there was no remaining drop in blood cell counts in the long term [59].

3.6 Fertility

Just like the red bone marrow, especially male gonadal tissue cells are highly proliferative and therefore generally susceptible to radiation. From external radiation therapy, it is known that this effect is cumulative.

In men, after I-131 therapy effects like an increased follicle stimulating hormone (FSH), an increased luteinizing hormone (LH) and oligospermia have been described in 20 to >50% of patients receiving high cumulative I-131 activities (13 GBq I-131 and more) [64]. Furthermore, after a single course of I-131 therapy, FSH and LH levels after 6 months are significantly elevated compared to baseline before returning to normal at 18 months post therapy, as an expression of transient impairment of testicular function [64]. Therefore, especially in patients with more advanced disease in whom higher cumulative I-131 activities can be foreseen, pre-therapeutic banking of sperm should be counselled to patients who have or may in the future develop the wish to conceive a child.

With regard to female fertility after I-131 therapy of thyroid cancer, Sawka et al. performed a meta-analysis of 16 studies on this topic [65]. Significant effects described in some studies were the presence of transitory menstrual irregularities, transitory hormonal changes in terms of elevated FSH and LH levels and the earlier, by approximately 1 year, onset of menopause.

3.7 Pulmonary Fibrosis

In patients with extensive lung metastases, and this especially concerns paediatric patients who may show a miliary pulmonary spread at diagnosis, the dose delivered to the lung parenchyma during I-131 therapy of DTC metastases may lead to pulmonary fibrosis, which is a potentially deadly complication of I-131 therapy in paediatric DTC [66]. In order to prevent this, it is advisable to regularly monitor pulmonary function in patients with pulmonary metastases and to refrain from further I-131 therapy in patients in whom a reduction in pulmonary function is suspected. Furthermore, safety of I-131 therapy can be increased by performing a dosimetry before administration of therapy, setting the limit at 3 GBq or 40 MBq per kg body weight whole body retention 48 h after administration of therapy.

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