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Controversies in the Radioiodine Treatment of Patients With Differentiated Thyroid Cancer

John Buscombe, MD, FRCP, FRCR

The use of radioiodine (I-131) in the management of patients suffering differentiated thyroid cancer (DTC) has changed little in the past 40 years. The use of a standardized approach has served the majority of patients well over that time. However, there have been recent doubts concerning this approach in some low risk patients and if so, how can these patients recognized and which patients who may need more intensive treatment.

A number of clinical trials have questioned the paradigms used in the treatment of DTC including what activity of I-131 should be used for ablation and which low risk patients should be treated with I-131 especially as there remains some doubts as to the long-term safety of I-131. Should a dosimetric approach be used to optimize the use of I-131 even though at present this approach has not been shown to improve outcomes in a formal clinical trial.

The era of precision oncology represents a challenge and opportunity to nuclear medicine with a move away from a regime of standard care to one of highly individualized care based on the genetic profiling of the patient and their cancer. The treatment of DTC with I-131 is about to become very interesting.

Semin Nucl Med 53:475-480

Introduction

Since the first work done by Saul Hertz over 7 decades ago[1-3] the role of I-131 in the treatment of differentiated thyroid cancer (DTC) has been central to control of this condition. However, as medicine moves into the era of applied genetics[4] and with a greater understanding of the mechanisms of cancer there is some doubt as to the future role in the management of this disease. Since the work by Mazaferri and Jhaing[5,6] it has been the received wisdom that DTC is best treated by complete thyroidectomy followed by ablation of all residual thyroidal tissue by I-131.[6,7] This approach was seen to reduce recurrent and death rates but these differences was best seen after 10 years from diagnosis by which time the numbers in follow up studies may be small.[5] Following such an approach thyroglobuloin a glycoprotein produced by normal thyroid cells should fall to zero. The thyroglobulin levels can then be used as a surrogate tumor marker (if the patient does not have antithyroglobulin antibodies). A rise in thyroglobulin will initiate a search for residual or metastatic disease and subsequent management which itself may include further cycles of I-131 and as such is the basis of most commonly used clinical guidelines[8-11] (Figs. 1 and 2).

Recently there has been some epidemiological work which has suggested that treatment with I-131 may not be as benign as previously thought and that there could be a risk of inducing secondary cancers.[12] This has led some groups, especially in Europe, to question the activity of I-131 administered and whether or not some patients with DTC have a risk of recurrence so low that they are unlikely to ever have recurrent or metastatic disease and therefore are being effectively over-treated with I-131.

There has been a renewed interest in whether a dosimetric approach would allow more precise dosing of I-131 and therefore increase efficacy and reduced the possibility of long-term effects by not over treating patients. The reliance of the sodium-(natrium) iodine-symporter (NIS) to import the radioiodine into the normal or cancerous thyroid cell has resulted in therapeutic escape from the therapeutic effects of I-131 by the cells not expressing NIS, this has been addressed historically by use of drugs like lithium[13] but without consistent results. The advent of new tyrosine kinase inhibitors (TKIs) has shown that re-expression of NIS may be induced allowing further I-131 therapies.[14]

Department of Nuclear Medicine, St Bartholemew's Hospital, London, UK.
Declaration of Competing Interest: None.
Address reprint requests to: John Buscombe MD, FRCP, FRCR, Department of Nuclear Medicine, St Bartholemew's Hospital, West Smithfield, London, EC1A 7BE, UK. E-mail: john.buscombe1@nhs.net

https://doi.org/10.1053/j.semnuclmed.2023.01.006
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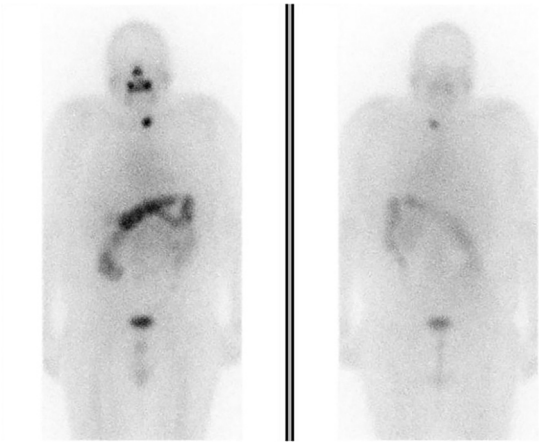

Figure 1 Whole body image performed following ablation of a "low risk" female patient of 23 years with a papillary thyroid cancer who has had a thyroidectomy. This patient received 30mCi (1.1GBq) I-131 and this 48 hour image shows a small amount of residual thyroidal tissue in the neck and no metastases Is this the best way to treat such a patient?

The impact of genetic profiling and the use of "liquid biopsies" to find circulating cancer cells will change the way cancer is followed up after initial treatment. This may lead to a paradigm shift in the way DTC is managed such that the use of adjuvant I-131 and the need for lifelong thyroxine support may no longer be the norm and I-131 will only be used in metastatic DTC.

Long Term Cancer Risk of I-131 Therapy

Despite 70 years of the safe use of I-131 in the treatment of DTC there remains some concerns that the radiation required to ablate residual thyroidal tissue or treat metastatic disease may induce a secondary primary cancer. An article published in 2018 a group of researchers in the USA reviewed the American surveillance, epidemiology and end results (SEER) database for those patients registered as suffering from differentiated thyroid disease and suffered a subsequent hematological malignancy.[12] This paper looked at the data of 148,215 patients with DTC of whom 47% received I-131 as part of their initial treatment. The determined there was a 1.79 hazard ratio for developing a secondary hematological malignancy if the patient had received I-131 compared to surgery alone. Further analysis showed there appeared only to be an increased risk for AML with a hazard ratio of 1.3 and CML with a higher hazard ratio of 3.9. The hazard ratio of developing multiple myeloma was only 0.65 which if true suggests prior I-131 has a protective effect. When looking at numbers of patients this meant that the risk of developing AML increased from 1.7/1,000 patients to 2.7/1,000 patients. Therefore, even if there is an increased risk, it remains small. For CML the risks appear higher 3.6/1,000 for patients having surgery to 6.2/1,000. There are several confounding factors which may result is errors including poor data fishing techniques, different patient groups receiving different treatments and the traditional use of hyperphysiological (itself carcinogenic-) thyroxine in patients treated with I-131.[15-17] The main issue with these types of papers is that while they can show an association, they cannot show causation. For example, CML is more common in the elderly, and we know from USA data that long term survival in DTC is improved if I-131 ablation follows surgery.[5,6] Therefore, it may be a higher risk of CML is because more patients treated with I-131 following surgery live long enough to get CML.

A cancer where there may be a clearer link is with breast cancer as female breast tissue can also express the NIS symporter and thus there could be a clear causal link. A recently published retrospective study from China looked at reported American cases of breast cancer of women who had been treated with or without I-131 (16,850 vs 22,135) for papillary and follicular thyroid cancer again using the SEER database.[18] The authors proposed a hazard ratio for developing a

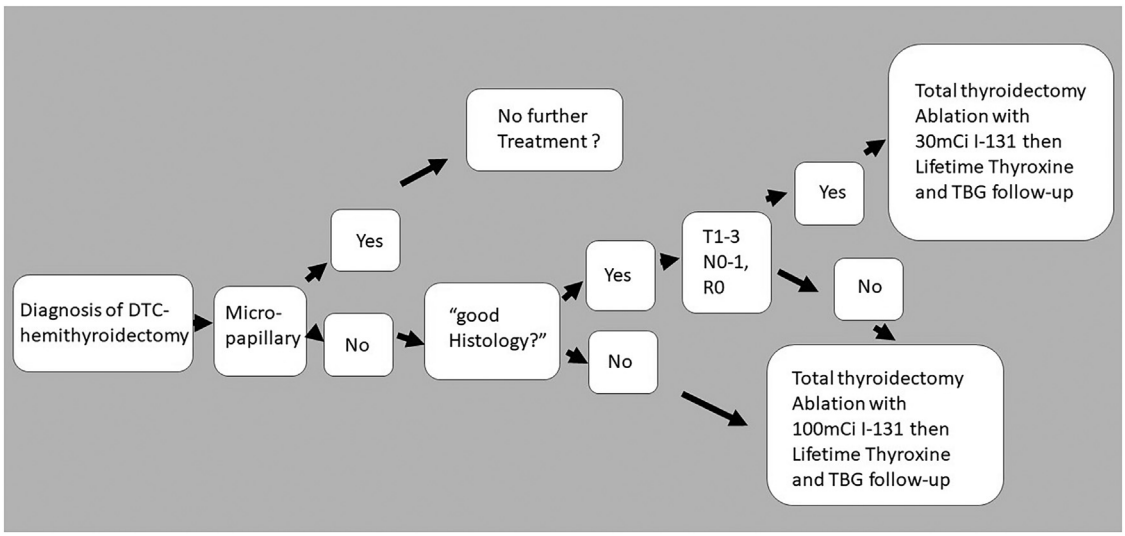

Figure 2 Treatment algorithm looking at present clinical guidelines for the initial treatment of differentiated thyroid cancer (DTC).[11]

secondary breast cancer if the patients had received I-131 when aged 15 to 39 of 1.65 but again there was no attempt to find a causal relationship. Again, like CML breast cancer is more common in elderly patients so those receiving I-131 postsurgery may have just been likely to survive long enough to develop breast cancer especially in some cases the breast cancer developed 35 years after the I-131 was administered. Also, in these data driven studies there is no attempt to identify the activity of I-131 administered and why it was used to supplement surgery especially as the surgery group may contain microadenomas or small T1 and T2 tumors.

The only way forwards is to run multicenter prospective data collecting trials where the use of I-131 is determined randomly, this raises significant ethical issues and is unlikely. Some attempts have been made in single centers, but the number of patients studied is just too small and the number of secondary breast cancers too infrequent for there to be any valid conclusion.[19] As this group included patients exposed to I-131 after a nuclear accident as well as medically administered I-131. However, it does seem logical that we question how much I-131 we should be administering and to whom and particularly in those patients with the lowest risk cancers.

How Much I-131 is Needed for Ablation

Ablation of the thyroid remnant has become the normal since the work of Mazeferri et al[5,6] have shown long term progression free survival was increased in patients who had received I-131 postsurgery. This had the advantage of removing any residual thyroglobulin producing normal thyroid cells so thyroglobulin could be used as a surrogate tumor marker.[11,20-24] A second theoretical advantage was any thyroid cancer which was not removed by a total thyroidectomy would also be treated. The activity administered was 100mCi (3.7GBq) and that standard had been used unchanged across the world until the 1990s. In view of the ongoing concerns especially outside of the USA about induction of secondary cancers there was increasing concern that 100mCi (3.7GBq) may not be the ideal activity to give in all patients especially as advances in ultrasound meant that an increasing number of patients were being diagnosed with T1 and T2 tumors.

A pilot study based in India looked at a range of ablation activities ranging from 25 to 200mCi (0.925-7.4GBq) and showed successful ablation rates were not dependent on activity given.[25] A follow-up study by the same group[26] demonstrated that for T1-T3 tumors with no nodal or metastatic disease a single dose of 25mCi (0.925GBq) or 50mCi (1.85GBq) was as effective in ablating post total thyroidectomy as an administered activity of 100mCi (3.7GBq). This was followed by a series of trials from around the world showing similar results though many of these trails were not randomized and the patient numbers were often too small to allow for statistical significance.[27-29]

Then in quick succession two multicenter phase III randomized control trials were performed one in the UK and the other in France. Both studies treated T1-3 tumors N0 or N1 with low-risk pathology. These were randomized to 30mCi (1.1GBq) vs 100mCi (3.7GBq).[30] In the UK study called HiLo 428 patients were recruited and the ablation rate from a single treatment was almost identical in the two groups (85% for 30mCi vs 87% for 100mCi). In the French study[31] patients were randomized to the same two activities and the ablation rate was identical at 92% for both the 30 and 100mCi (1.1 and 3,7GBq) activities. A more recent long term follow-up study has shown 5 year recurrence rates were also similar for the two administered activities with 2.1% for 30mCi (1.1 GBq) and 2.7% for the 100mCi (3.7 GBq) group in the UK study with a similar rate in the French study.[32,33] This confirms that for low-risk patients the use of lower activity I-131 is just as effective and carries no increased risk of later recurrence. This has results in adoption of these activities into UK clinical guidelines.[11]

There has been resistance to applying these results in other countries partly lead by the variable quality of thyroid surgery. Critics of these studies point out both UK and France have highly centralized cancer services meaning thyroid surgery is carried out by a small number of highly skilled surgeons a situation which is not universal and as such many communities feel happier to continue to give higher activities of I-131 in postsurgical ablation.

Should We Treat Small Low Risk DTC With I-131 Ablation?

A further question concerns whether-or-not patients with small T1 tumors require any treatment with I-131. It has become general practice not to treat patients with low-risk micropapillary carcinomas with any surgery beyond a hemithyroidectomy[8,9] however, the treatment of small T1 and T2 tumors which have low risk pathology remains controversial. A prospective phase III multicenter RCT from France looked at T1 and T2 which were randomized to receive total thyroidectomy or total thyroidectomy plus 30mCi (1.1GBq) I-131 in a ratio of 1:1. A total of 730 patients were recruited and the rate of recurrent or residual disease by three years was 4.4% in the total thyroidectomy group and 4.1% in the thyroidectomy and thyroidectomy and I-131 group.[34] The main predictor of recurrence being a post-total thyroidectomy was a thyroglobulin of greater than 1 ng/mL. Despite concerns that the nodal status was not established before randomization this study has been incorporated into the latest UK guidance.[11] Further data should become available after the publication of the ION study.[35] However, the prior concerns of the quality of surgery in some centers compared to those available in France and the UK may limit the wider adoption of what many may see as too radical an approach to treatment of thyroid cancer.

Patient Preparation Thyroid With-Drawl or Recombinant TSH and

The arrival of recombinant thyroid stimulating hormone rTSH allowed for an alternative to the traditional method of preparing patients for treatment with I-131 by withdrawing

thyroxine support for up to 28 days which could leave many patients in significant distress.[36]

Within both the HiLo and ESTIMABL1 studies there was a further randomization to prior thyroid with-drawl or pretherapy use of recombinant TSH (rTSH). The recurrence rates in the HiLo study was 1.5% for rTSH vs 2.1% for thyroxine with-drawl at 3 years and 2.1% for rTSH vs 2.7% for thyroxine with-drawl at 5 years.[30] Similar results were seen in ESTIMABL1.[31] Nonrandomized, single and multicenter studies show similar results in Germany and Italy with longer follow-up periods up to 10 years.[37,38] A follow-up study of the HiLo group did show a nonsignificant increased recurrence rate among those receiving rTSH (8.3%) vs 5.0% for thyroxine with-drawl at 7 years.[34,35] As expected, the side effects of the rTSH were minimal compared to thyroxine with-drawl but an attempt in the UK NICE to quantify if this was a cost-effective strategy failed as it was not possible to quantify non-medical costs such as days off work or substandard working which occurred in the thyroxine with-drawl group but rarely seen in the rTSH group.[11] This is frustrating but these costs are generally borne by the patient or their employer and not the state of health insurance company. Compounding this situation is that the cost of rTSH for health systems is significantly higher than thyroid with-drawl. Also, presently there is a paucity of evidence for the use of rTSH in treating metastatic thyroid cancer with higher activities of I-131 and it is not included in its product license However, many centers will use rTSH in such patients especially is elderly patients or those with known cardiovascular disease.

The Role of Dosimetry

A criticism of the present use of I-131 is that treatment is activity based and not related to either thyroid remnant or tumor-based dosimetry.[39] Though several medical societies have voiced their support for a dosimetric based treatment for all cancers using radionuclides,[40] this has not been supported internationally for example, the most recent joint SNMMI and EANM thyroid guidelines merely suggest this approach as an alternative to a risked based approach based on pre-therapy scanning.[9] This risk stratification proposed by Avram et al[41,42] uses a pretherapy I-123 SPECT/CT or I-124 PET/CT to look at disease load and then adapt the initial activity given from 30 to 200mCi (1.1 = 7.4GBq). However, these conclusions are based on a series of single site retrospective reviews. Therefore, neither a dosimetric approach or a risk adjusted approach based on pretherapy scanning has been tested by a prospective multicenter phase III trial though both techniques could well be tested in such a way. Therefore, until such a trail has been undertaken and reported clinical guidelines cannot fully endorse such as approach.[11]

Use of Drugs to Restart NIS

One of the issues with treatment of metastatic thyroid cancer has been the issue of loss of the trapping and organification of iodine leading to escape of the tumor from radioiodine treatment. This is thought to be due to reduced or nonexpression of the NIS. There have been various attempts to restore the expression of NIS primarily using lithium and vit A analogies such as Bexarotene however, there has never been any consistent results suggesting either of these approaches are clinically useful.[13,43,44] However, the discovery that both anaplastic thyroid cancers and metastases without expression of NIS often have a mutant protein kinase (BRAF) gene (BRAF-V600E) has resulted in the use of Tyrosine kinase inhibitors (TKIs) with specific BRAF inhibitor such as Dabrafenib.[45] This drug was initially used in BRAF-V600E positive melanoma but has been used in anaplastic and noniodine avid DTC which express BRAF-V600E.[46,47] A paper published in 2015 from a single site open label trial of the Dabrafenib use 6 of 10 patients in whom their DTC no longer accumulated Iodine was shown to have redifferentiated and were now iodine avid. A different approach has been reported using the mitogen-activated protein kinase (MAPK) inhibitor TKI selumetnib which redifferentiated 8 of 12 patients with previous iodine negative DTC sufficiently to allow for treatment with I-131, 5 of these patients had a good partial response. The advantage of this approach is that it did not depend on the presence of the BRAF-V600E mutation.[14] Similar results have been reported using another MAPK inhibitor Larotrectinib[48] An extension of this idea is to use these types of drugs to enhance uptake of I-131 even those patients in whom the DTC is still iodine avid. A small trial has just reported in 5 patients a combination of a short course of a vemurafenib (another BRF inhibitor) and an anti ErbB3 antibody CDX-3379 increased uptake of Iodine-131 in 4 of 7 patients, 2 of which went on to have a good partial response.[49] These are small studies but do show that combinations of selected Iodine-131 and selected TKIs may become the norm for patients with advance, high risk or stage 3 and 4 DTC.

Possible Genetic Testing Replacing TBG

The present logic for ablation of the thyroid remnant requiring life-long thyroxine is to enable the use of plasma thyroglobulin a rise of which would trigger further investigations and treatment. However, this approach requires treating all patients in the same way when only a minority may suffer recurrence or metastatic disease. An alternate is to look at levels of microRNA within the blood. These are small segments of RNA which do not code but are used for cell signaling and a range of these are up or down regulated in both papillary and follicular thyroid cancer.[50] Initially these were used primarily on cytogenic material and are offered as an alternative to surgery in providing a definitive diagnosis of thyroid cancer in the USA.[51] Their use is controversial and not recommended in clinical guidelines.[11] These microRNA assays offer the theoretical advantage that they can be detected in blood and could be used to monitor the disease in patients without the need

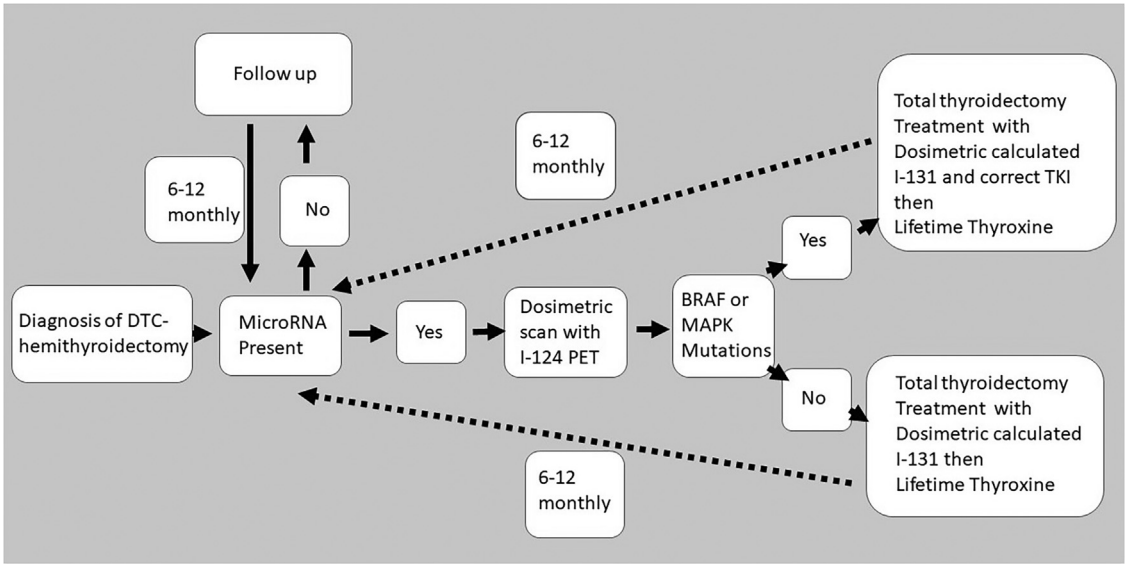

Figure 3 Possible future algorithm where patients with DTC who are risk assessed using micoRNA to identify if any cancer cells are present and genetic markers of BRAF and mitogen-activated protein kinase (MAPK) to determine if tyrosine kinase inhibitors TKIs should be used with the correct calculated activity of I-131 to destroy all the tumor present as found on I-124 PET.

for total thyroidectomy and I-131 ablation.[52] Further to this if and when such recurrence occurs different microRNAs will predict whether or not the patient will respond to I-131 or has a mutant BRAF or mutant MAPK such that specific TKIs should be used instead or in combination with I-131.[53]

Conclusion

The revolution that is coming to all cancer treatments with the rise of genomic medicine will have a profound effect on the way we manage thyroid cancer (Fig. 3). Nuclear medicine needs to embrace these changes and adapt to use the knowledge gained through clinical trials to optimize treatment. The days of "one treatment fits all" is disappearing and nuclear medicine needs to adapt to the new world of personalized and precision medicine which will revolutionize the care of patients with DTC in the decades to come.

Acknowledgments

The author was not funded by any organization or commercial company.

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