Original Paper

Clinical Practice Guideline for Management of Well-differentiated Thyroid Carcinoma. Songklanagarind Consensus [Part 1]

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Abstract

Background: *Clinical practice guideline (CPG) is one of the processes whereby a consensus in a management (usually of a disease or groups of diseases) is ob tained by evidence-based dialogue. Well-differentiated thyroid cancer (WDTC) is still one of the diseases where treatment, especially related to I-131, varied. This is probably because of its relatively low complication rate and the lack of controlled trial.*

Methods: *The 3 nuclear physicians modified their practices so that there is a consensus in the post-surgical management of WDTC, choosing initially an uncomplicated one. Agreements were subtantiated by literature review. This CPG was practiced for one year resulting in this report.*

Recommendation: *After surgery, patients with WDTC would be given baseline measurement such as thyroglobulin, thyroglobulin antibody and then ablated as an outpatient with 30 mCi I-131 without pre-ablative diagnostic total body scan. The ablation could be repeated up to 3 times and then the patient observed or given larger I-131 dose as an inpatient if there was persisting thyroid residue. Thyroglobulin should always be obtained under maximum thyroid stimulation.*

Thyroxine at 200 µg would be maintained daily if this dose could be tolerated. Following one years' practice of the CPG, we decided to increase our diagnostic TBS dose to circumvent the occasional missed thyroid residue or recurrence or a metastasis.

Key words: *Thyroglobulin (Tg), total body scan (TBS), I-131, thyroxine (T4), thyroid stimulating hormone (TSH).*

INTRODUCTION

The management of well-differentiated thyroid carcinoma (WDTC) with iodine-131 (I-131) after surgery is still controversial[1-9] despite the use of such therapy for more than 50 years. There had been no well-controlled trial as a guide. The varied regimens in managment of thyroid cancer rested essentially on historical reports

with their multitudes of interrelated factors such as: age, gender, histology, dose of iodine-131 and duration of follow-up. At present, there is still a lack of consensus in several aspects of the routine treatment of WDTC. Examples of this include: the necessity for pre-ablative iodine-131 total body scan (TBS) after surgery, the choice of low dose (30 mCi) versus high dose (100 mCi) I-131 for thyroid ablation, whether monitoring of thyroglobulin (Tg) should be done while off or on thyroxine (T4) or how often should routine TBS be ordered. These decisions affect the financial and human load on health care. Poor decision would be costly without benefit to the patient.

The present report is a consensus from our nuclear medicine physicians in the routine treatment of postoperative WDTC. The consensus was agreed on 12 months previously and this report incorporates our additional modification after a year of practice. It is hoped that such consensus would provide a uniform management to any patient independent of which nuclear medicine physician was in charge at the different visits. Such format may also facilitate referral from surgeons from different institution. Finally, it is hoped that such a report would encourage other nuclear medicine facilities to set up their own guidelines and eventually a national guideline from the society itself, a guideline that takes into account the characteristic and environment of Thailand.

PROCEDURE

The clinical scenario agreed on was a patient with WDTC referred from the surgeon. We set this scenario because it is the most common in our practice.

It was assumed that there would be a full surgical report with a formal detailed histology. [if these were not present, they had to be requested]. From this scenario, the nuclear medicine physicians raised questions pertained to the management. Such questions would be: what investigations are needed when first seen; whether a pre-ablative diagnostic TBS to evaluate the presence of thyroid remnant is necessary and why; what should be the dose of I-131 for ablation of remnant; how often is diagnostic TBS necessary to confirm successful ablation and how frequent is diagnostic TBS necessary in monitoring patients; should thyroglobulin (Tg) level be obtained under maximum drive of thyroid stimulating hormone (TSH) and the benefit of thyroxine (T4) in dose that is tolerable (rather than purely for replacement) to suppress cancer spread.

For each question raised with regards to management, the physicians offered their answers and the accompanying reasons. If there was an agreement, this was written down. Subsequently, literature support had to be supplied. If there was a disagreement, then the literature support had to be obtained and discussed such that a consensus can be reached and this written down. The draft was circulated and further discussed. The agreed procedure was then practised. The style of our practice is such that a patient is not restricted to one nuclear medicine physician. At the same time all physicians have equal access to the patient and medical record either in the pre-planning stage of the management which was done a month prior to the visit or in the actual evaluation of the patient when physically seen. Thus the guideline was, in a way, routinely cross-checked. One year later, the initial consensus was evaluated and new suggestions added. These are included in this report.

RECOMMENDATIONS

1. Prior to I-131 ablation

1.1 The patient would wait at least 6 weeks post-operatively without thyroid hormone replacement such that the elevated TSH will stimulate uptake by the thyroid remnant[10]. The appropriate TSH for maximal benefit from ablation is not really known. The often quoted 30 µIU/ml was recommended by Edmonds et al.[11] without specific support, assuming that a tumor would be incapable of concentrating I-131 adequately unless serum TSH exceeded that level. Wyngaarden and Mcdougall[12] reported that TSH > 10 µIU/ml at the time of first scan was associated with successful ablation (uptake < 0.3%) in 93% of patients. Faced with this dilemma and inconvenience, we do not use TSH level in deciding ablation of thyroid remnant.

1.2 The patient should have been on low-iodine diet for 1 week to enhance the remnant uptake. Maxon et al.[13] reported that restricted iodine intake can lower iodine excretion from 346.9 to 42.8 µg/g of creatinine per day with an apparent increase in the radiation dose to the thyroid tissue per millicurie of administered I-131.

1.3 Routine measurement of serum Tg with TSH and thyroglobulin antibody (TgAb) was recommended. High Tg might reflect metastases. Filesi et al.[14] reported that initial Tg greater than 60 mg/ml was seen in two-thirds of the patients with metastases. TSH and TgAb provided confidence in using Tg as a marker. Serum Tg determined during TSH suppression would not predict the presence of persistent or recurrent thyroid cancer[15-21] when compared to Tg obtained during maximal TSH stimulation. TgAb could interfere with the measurement of Tg either giving falsely high or low values depending on the method of measurement[22]. We accepted the argument that these routine measurements might have a low yield since residual thyroid can elevate Tg and at the same time prevent adequate elevation of TSH. Also it was reported that TgAb fell with duration of follow-up such that low or undetectable levels would be seen before the second post-operative year in the disease-free group[22]. However, we thought that screening for the few cases with true elevation of Tg (reflecting metastasis) might help in planning early high dose therapy.

1.4 Routine chest roentgenogram (CXR) would be done (if no recent one was available such as seen in cases sent from distant medical centers), despite its doubtful cost-benefit in low-risk patients. Martins et al.[23] reported that initial CXR revealed metastases in only 2%. However, with the low cost of CXR, it might be advantageous to pick up other abnormalities in the thorax such as cardiac enlargement or other parenchymal lung diseases.

1.5 The patient and relatives would be given detailed instructions as well as pamphlets on minimizing

radiation to family members and to the population at large. In applicable instances, caution with regard to pregnancy would be discussed.

2. I-131 ablation

2.1 We agreed to directly ablate the remnant with no pre-ablative TBS for the following reasons: a) It was rare in our practice not to detect thyroid remnant after all types of thyroid surgery[24]. Hence ablation for remnant had always been routine. b) This higher I-131 dose might facilitate detection of metastases. However, with a large thyroid remnant, the ability to detect small metastasis might be independent of dose of I-131 used for TBS since most radioactivity would be concentrated at the thyroid[25-27]. c) Diagnostic dose of I-131 from pre-ablative TBS might also delay ablative therapy because of thyroid stunning. Some authorities[28-30] reported that a scanning dose of 3 mCi can produce stunning ranging from 12.8-40% of the patients while the time intervals for detecting this stunning ranged from 1 week to 1 month.

2.2 The ablative dose agreed on was 30 mCi of I-131, the maximum permissible dose for an outpatient treatment. Such dose is convenient and economical. It had been shown to be as effective as a higher dose. The table summarizes percentage success in ablation after a single low dose I-131. Complete ablation was achieved in 58% to 90%. Rate of successful ablation were similar when compaing low and high dose I-131 [81% versus 84%[35], 63% versus 78%[37] and 82%, for low versus 83% for high respectively[38]].

[There was an exception to the scheme for routine ablation. We decided not to ablate a female who was less than 45 years old and had a single and small papillary tumor. Most authorities[39-43] advocated that ablation was not necessary in low-risk patients as defined by Cady and Rossi[41]. After one-years' practice we found only 1 very low risk patient and hence had not

Table *Success rate of low-dose iodine ablation*

Study group reference	No of patients	Ablative dose (mCi)	Percent success af first ablative
McCowen (1976, 31)*	36	25-29	58
DeGroot (1982, 32)	18	30	83
Synder (1983, 33)	69	29	81
Creutzig (1987, 34)	10	30	70
Johansen (1991, 35)	26	29	81
Leung (1992, 36)	69	30	90
Bal (1996, 37)	27	25-35	63
Wyngaarden (1996, 12)	60	29	80
Lin (1998, 38)	25	30	82**

* = (year of report, reference number),
** = with 2 and 3 doses the success went up to 92 and 94% respectively[38].

extend our definition for cases not needing I-131 ablation. If there were more of these patients we would have to decide on how to follow these patients, and how we would interpret their slight rise in Tg. There had been no report on long-term management of this group].

3. Thyroid hormone

All patients would receive thyroid hormone replacement. We agreed to maintain at least 200 µg/day of T4 (thyroxine) if this could be tolerated. Hoffman et al.[44] and Lambert et al.[45] reported that the dose of T4 required to completely suppress serum TSH (defined as absence of response to TRH stimulation test) varied from 150 to 300 µg/day with a mean of about 225 µg/day. We did not routinely measure TSH levels while our patient was on T4 unless there were suggestions of hyperthyroidism. Such test is still relatively costly and the procedure is inconvenient since it needed an extra attendance. Interestingly there had been no report of the range of TSH among those given 200 µg/day of T4.

4. Total body scan

TBS would be done 5 days after ablation.

4.1 If the TBS showed metastases or local spread, the patient would be given a high dose treatment in an isolation room 3-6 months later. We assumed that a 3 month interval would be adequate for most of the residual thyroid to have been ablated and at the same time, the residue, local spread or metastases would not be susceptible to stunning.

4.2 If ablative TBS showed only thyroid remnant, the patient would be routinely followed.

5. Follow up

Post-ablatively, the patient would be evaluated at 6 and 18 months with diagnostic (2 mCi of I-131) TBS and serum Tg measured under maximum TSH stimulation. The number of TBS and the interval between TBS appeared arbitrary but sensible[25-27,40]. The diagnostic TBS dose of 2 mCi of I-131 also seemed sensible and had been reported not to produce stunning[28,46]. We now plan to increase our diagnostic TBS dose to 3-5 mCi since in some cases, we missed picking up small thyroid remnants, despite care in performing TBS. [NB. We are not certain the importance of missing minimal remnants when maximum TSH can be achieved]. Due to administrative constraints, we never can re-ablate or give high I-131 dose within 2 months of the diagnostic-TBS, hence avoidance of stunning with 5 mCi diagnostic TBS should not be a problem. Maximum TSH stimulation was provided by discontinuing T4 for 6 weeks and triiodothyronine (T3) for 2 weeks. Hilts et al.[10] reported that TSH was significantly elevated within 2 weeks after T3 withdrawal and Edmonds[11] reported that TSH remained normal for as long as 4 weeks after stopping T4. We measured Tg only at maximum TSH stimulation. T4 replacement would be reinstituted 3-4 days after I-131 was given, to allow maximum iodine absorption.

5.1 If TBS still showed remnant thyroid after 3 ablations we agreed to give high dose I-131. The cutoff at 3 ablations was purely arbitrary judging from the reports of Lin et al.[38] and Johansen et al.[35] that thyroid remnants would still respond after the second ablation. In this matter of response to the

first ablation, it might be interesting to compare TSH level between those that failed or those who responded to the single ablation.

5.2 If TBS revealed minimal uptake in the thyroid bed while the TSH was maximum (arbitrarily chosen as greater than 50 µlU/ml), we would define that as complete ablation. Hurley and Becker[25] suggested that repeat ablation should not be necessary in patients without residual thyroid cancer if TSH was over 30 µIU/ml and TBS was negative, even the uptake in the thyroid bed was greater than 1% at 48 hours. We have not been measuring thyroid uptake in WDTC.

5.3 If 2 successive diagnostic TBS were negative then the patients would enter our regimen of long-term follow-up which consisted of yearly neck examination and Tg measurement under maximum TSH stimulation. Our new consensus among those with persistently low Tg (under maximum TSH) is that such Tg will only be measured every 2 years. Routine CXR would not be requested unless suspicious[24, 47-48]. The appearance of new nodes, elevated Tg etc. would be discussed in the next chapter.

REFERENCES

1. Samaan N, Schultz PN, Hickey RC, et al. The results of various modalities of treatment of well differentiated thyroid carcinoma: A retrospective review of 1599 patients. *J Clin Endocrinol Metab* 1992;75:714-20.
2. Singer PA, Copper DS, Daniels GH, et al. Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. American Thyroid Association. *Arch Intern Med* 1996;156:2165-72.
3. Solomon BL, Wartofsky L and Burman KD. Current trends in the management of well differentiated papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1996;81:333-9.
4. Raynolds JC and Robbins J. The changing role of radioiodine in the management of differentiated thyroid cancer. *Semin Nucl Med* 1997;27:152-64.
5. Yeh SD and La-Quaglia MP. I-131 therapy for pediatric thyroid cancer. *Semin Pediatr Surgery* 1997;6:128-33.
6. Paloyan E, Walker RP and Lawrence AM. Guidelines for the use of radioiodine, thyroid hormone and treatment of metastatic disease in patients with differentiated cancer. *Surg Oncol Clin N Am* 1998;7:665-80.
7. Taylor T, Specker B, Robbins J, et al. Outcome after treatment of high-risk papillary and non-Hurthle cell follicular thyroid carcinoma. *Ann Intern Med* 1998;129:622-7.

8. Vanderpump MP, Alexander L, Scarpello JH, et al. An audit of the management of thyroid cancer in a district general hospital. *Clin Endocrinol (Oxf)* 1998;48:419-24.

9. Sherman SI. Adjuvant therapy and long-term management of differentiated thyroid carcinoma. *Semin Surg Oncol* 1999;16:30-3.

10. Hilts SV, Hellman D, Anderson J, et al. Serial TSH determination after T3 withdrawal or thyroidectomy in the therapy of thyroid carcinoma. *J Nucl Med* 1979;20:928-32.

11. Edmonds CJ, Hayes S, Kermode JC, et al. Measurement of serum TSH and thyroid hormone in the management of treatment of thyroid carcinoma with radioiodine. *Br J Radiol* 1977;50:799-807.

12. Wyngaarden MV and McDougall IR. What is the role of 1110 MBq (< 30 mCi) radioiodine I-131 in the treatment of patients with differentiated thyroid cancer? *Nucl Med Commun* 1996;17:199-207.

13. Maxon HR, Thomas SR, Boehringer A, et al. Low iodine diet in I-131 ablation of thyroid remnants. *Clin Nucl Med* 1983;8:123-6.

14. Filesi M, Alberto S, Ventroni G, et al. Role of initial iodine-131 whole body scan and serum thyroglobulin in differentiated thyroid carcinoma metastasis. *J Nucl Med* 1998;39:1542-6.

15. Ng TFDC, Hoffenberg R, Maidey MN, et al. Serum thyroglobulin concentrations and whole-body radioiodine scan in follow-up of differentiated thyroid cancer after thyroid ablation. *BMJ* 1979;2:298-300.

16. Schlumberger M, Charbord P, Lumbroso J, et al. Circulating thyroglobulin and thyroid hormones in patients with metastases of differentiated thyroid carcinoma : relationship to serum thyrotropin levels. *J Clin Endocrinol Metab* 1980;51:3-9.

17. Girelli ME, Busnardo B, Amerio R, et al. Critical evaluation of serum thyroglobulin (Tg) levels during thyroid hormone suppression therapy versus Tg levels after hormone withdrawal and total body scan: results in 291 patients with thyroid cancer. *Eur J Nucl Med* 1986;11:33-5.

18. Hershman JM and Edwards CL. Serum thyrotropin (TSH) levels after thyroid ablation compared with TSH levels after exogenous bovine TSH: implications for 131-I treatment of thyroid carcinoma. *J Clin Endocrinol Metab* 1972;34:814-8.

19. Pacini F, Lari R, Mazzeo S, et al. Diagnostic value of a single serum thyroglobulin determination on and off thyroid suppressive therapy in the follow-up of patients with differentiated thyroid cancer. *Clin Endocrinol* 1985;23:405-11.

20. Landenson PW, Bravemen LE, Mazzaferri El, et al. Comparison of administration of recombinant human thyrotropin with withdrawal

of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. *N Eng J Med* 1997;337:889-96.

21. Duren M, Siperstein AE, Shen W, et al. Value of stimulated serum thyroglobulin levels for detecting persistent or recurrent differentiated thyroid cancer in high-and low-risk patients. *Surgery* 1998;126:13-9.
22. Spencer CA, Takeuchi M, Kazarosyan M, et al. Serum thyroglobulin antibodies: Prevalence, influence on serum thyroglobulin measurement and prognostic significance in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1998;83:1121-7.
23. Martins RG, Caplan RH, Lambert PJ, et al. Management of thyroid cancer of follicular cell origin:Gundersen/Luntheran Medical Center, 1969-1995. *J Am Coll Surg* 1997;185:388-97.
24. Cholewinski SP, Yoo KS, Klieger PS, et al. Absence of thyroid stunning after diagnostic whole-body scanning with 185 MBq I-131. *J Nucl Med* 1998;41:1198-202.
25. Hurley JR and Becker DV. Treatment of thyroid carcinoma with radioiodine. In: Gottschalk A, Hoffer PB and Potchen EJ eds. *Diagnostic Nuclear Medicine* Vol. 2.2nd ed. Baltimore: Williams & Wilkins, 1988;792-817.
26. Mazzaferri EL. Radioiodine and other treatments and outcomes. In: Braverman LE and Utiger RD eds. Werner and Ingbar's *The thyroid* 7th ed. Philadelphia: Lippincott-Raven, 1996:922-45.
27. Harbert JC. Radioiodine therapy for differentiated thyroid carcinoma. In: Harbert JC ed. *Nuclear Medicine Therapy*. New York: Thieme Medical Publishers, 1987;37-89.
28. Muratet JP, Daver A, Minier JF, et al. Influence of scanning doses of iodine-131 on subsequent first ablative treatment outcome in patients operated for differentiated thyroid cancer. *J Nucl Med* 1998;39:1546-50.
29. Park HM, Perkins OW, Edmonson JW, et al. Influence of diagnostic radioiodine on the uptake of ablation iodine-131. *Thyroid* 1994;4:49-54.
30. Kao CH and Yen TC. Stunning effects after a diagnostic dose of iodine-131. *Nuklearmedizin* 1998;37:30-2.
31. McCowen KD, Adler RA, Ghaed N, et al. Low dose radioiodine thyroid ablation in post surgical patients with thyroid cancer. *Am J Med* 1976;61:52-8.
32. DeGroot LJ and Reilly M. Comparison of 30 and 50 mCi doses of I-131 for thyroid ablation. *Ann Intern Med* 1982;96:51-3.
33. Synder J, Gorman C and Scanlon P. Thyroid remnant ablation: questionable pursuit of ill-defined goal. *J Nucl Med* 1983;24:659-65.

34. Creutzig H. High or low dose radioiodine ablation of thyroid remnants. *Eur J Nucl Med* 1987;12:500-2.

35. Johansen K, Woodhouse NJY and Odugbsan O. Comparison of 1073 and 3700 MBq I-131 in postoperative ablation of residual thyroid tissue in patients with differentiated thyroid cancer. *J Nucl Med* 1991;32:252-4.

36. Leung SF, Law MWM and Ho SKW. Efficacy of low dose iodine-131 ablation of post-operative thyroid remnants: a study of 69 cases. *Br J Radiol* 1992;65:905-9.

37. Bal CS, Padhy AK, Jana S, et al. Prospective randomized clinical trial to evaluate the optimal dose of I-131 for remnant ablation in patient with differentiated thyroid carcinoma. *Cancer* 1996;77:2574-80.

38. Lin JD, Kao PF and Chao TC. The effects of radioactive iodine in thyroid remnant ablation and treatment of well differentiated thyroid carcinoma. *Br J Radiol* 1998;71:307-13.

39. Mazzaferri EL and Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994;97:418-28.

40. Schlumberger MJ. Papillary and follicular thyroid carcinoma. *N Engl J Med* 1998;338:297-306.

41. Cady B and Rossi R. An expanded view of risk group definition in differentiated thyroid carcinoma. *Surgery* 1988;104:947-53.

42. McHenry C, Jarosz H, Davis M, et al. Selective postoperative radioactive iodine treatment of thyroid carcinoma. *Surgery* 1989;106:956-9.

43. Hay ID, Grant CS, van Heerden JA, et al. Papillary thyroid microcarcinoma: A study of 535 cases observed in a 50-year period. *Surgery* 1992;112:1139-46.

44. Hoffman DP, Surks MI, Oppenheimer JH, et al. Response to thyrotropin releasing hormone; an objective criterion for the adequacy of thyrotropin suppression therapy. *J Clin Endocrinol Metab* 1977;44:892.

45. Lamberg BA, Rantanen M, Saarinen P, et al. Choosing thyroxine dose after treatment of thyroid cancer. *Lancet* 1977;2:1290-1.

46. McDougall IR. 74 MBq radioiodine 131I does not prevent uptake of therapeutic doses of 131I in differentiated thyroid cancer. *Nucl Med Commun* 1997;18:505-12.

47. Schlumberger M, Tubiana M, De Vathaire F, et al. Long-term results of treatment of 283 patients with lung and bone metastasis from differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1986;63:960-3.

48. Lorenzen J, Beese M, Mester J, et al. Chest X-ray: routine indication in the follow-up of differentiated thyroid cancer? *Nuklearmedizin* 1998;37:208-12.