CLINICAL STUDY

Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients

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Abstract

Objectives: Currently, little is known about the prognostic significance of achieving successful ablation with the first dosage of I-131 in patients with differentiated thyroid cancer. This study aimed to assess the following: (i) whether successful or unsuccessful ablation at post-ablation follow-up has prognostic consequences; (ii) possible factors predicting success of ablation in a patient.

Methods: In order to do this, we retrospectively studied 180 patients with a median follow-up of 55 months. Ablation was considered to be successful if 1 year after the initial dosage of I-131 patients fulfilled all of the following criteria: not dead from thyroid cancer, no additional therapy needed for any kind for thyroid cancer within the first year, undetectable thyroglobulin (Tg) levels under TSH stimulation, and negative I-131 scintigraphy. Tg levels at the time of ablation ($P < 0.001$), lymph node metastasis ($P = 0.04$) and distant metastasis ($P < 0.001$) have a significant influence on the success of ablation. P values were calculated by Mann–Whitney U test and Chi-square test, respectively.

Results: Patients with successful ablation had a better prognosis than those with unsuccessful ablation: disease-free survival was 87% versus 49% after 10 years; additionally, thyroid-cancer related survival was 93% versus 78%.

Conclusion: We conclude that the extent of the remaining normal or neoplastic thyroid tissue influences the outcome of ablation, and that successful ablation leads to a better prognosis. It seems that it is very important to achieve complete ablation as soon as possible in order to ensure the best possible prognosis for a patient.

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Introduction

Treatment of differentiated (papillary or follicular) thyroid cancer consists of thyroidectomy and an ablative dosage of iodine-131 (1). The addition of I-131 ablation, after surgery, leads to a significantly improved prognosis, especially in patients who are at high risk of recurrence of or death by thyroid cancer (2–6). Unfortunately, the first dosage of I-131 is not always sufficient to achieve complete ablation of thyroid remnants (7–13).

This study aimed to assess the following: (i) whether successful or unsuccessful ablation at post-ablation follow-up has prognostic consequences; (ii) possible factors predicting success of ablation in a patient.

To be included in this study, at least one of the following criteria had to apply:

- The patient returned for diagnostic scintigraphy and measurement of thyroglobulin (Tg) levels during thyroid-stimulating hormone (TSH) administration (Tg off) 1 year after ablation.
- The patient had received an additional therapeutic dosage of I-131 within the first year following the ablative dosage of I-131.
- The patient died of thyroid cancer within the first year following the ablative dosage of I-131.

Out of 192 eligible patients, 180 met at least one of these criteria. The patient characteristics are given in Table 1.

Patients, materials and methods

Patients

All patients with differentiated thyroid carcinoma referred to our centre for their first, ablative dosage of I-131 after 1 January 1990 were reviewed retrospectively.

Initial treatment

All patients underwent (near) total thyroidectomy, and received an ablative dosage of I-131 4–6 weeks after thyroidectomy. Between surgery and ablation, patients did not receive levothyroxine (LT4) supplementation, and they were instructed to have a low-iodine diet for

Table 1 Patient characteristics.

<i>n</i>	180
Mean age in years (range)	46 (14–84)
Female/male	126/54
Papillary/follicular	123/57

1 week (5 days before and 2 days after I-131 administration) (14).

To prevent 'stunning' of thyroid remnants (15–17), no diagnostic scintigraphy was performed before the administration of the ablative dosage of I-131. Patients were treated according to a fixed dosage protocol: 3700 MBq of I-131 in cases without known lymph-node or distant metastasis, 5550 MBq of I-131 in cases of pre- or perioperatively detected nodular involvement, or 7400 MBq of I-131 in cases of known distant metastasis.

Follow-up after ablation

In our department, patients that are treated for differentiated thyroid carcinoma are usually evaluated by the measuring of Tg levels and whole-body scintigraphy using 370 MBq I-131 1 year after administration of the ablative dosage, which happens after LT4 withdrawal for 4 weeks. In all but four patients, this resulted in TSH levels of >30 mU/l, with a maximum of 469 mU/l.

Ablation was considered to be successful if, 1 year after the initial dosage of I-131, patients fulfilled all of the following criteria:

- not dead from thyroid cancer
- no additional therapy needed for any kind for thyroid cancer within the first year
- undetectable Tg levels under TSH stimulation
- negative I-131 scintigraphy.

Tg levels were not used as a criterion for success of ablation in the cases when a patient tested positive for the presence of Tg antibodies, since test results for Tg cannot be considered reliable in these patients (18, 19).

Disease-free interval, recurrence and survival

A disease-free patient was considered to have a recurrence if one or more of the following conditions developed:

- detectable Tg levels
- pathological evidence of disease, as by fine-needle aspiration biopsy
- positive I-131 scintigraphy.

In our analysis, the disease-free interval started at the time of the first completely negative follow-up. This could be at the time of the 1-year post-ablation scintigram (as in the group with successful ablation),

or at a later follow-up scintigram if a patient required additional treatment to become free of disease (as in the group with unsuccessful ablation). Disease-free survival was considered to end at the moment of detection of a sign of recurrence. Thyroid-cancer specific survival was considered to start at the moment of administration of the ablative dosage of radioiodine.

Statistical analysis

For statistical analysis, we used SPSS Version 10.1 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was shown with $P < 0.05$. For testing between different groups of patients, the Mann–Whitney test (Z approximation) was used if one of the variables involved was continuous. The chi-square test was used if both variables involved were categorical data. Survival times were analysed by the method of Kaplan–Meier. Additionally, the difference between survival curves was examined by the log rank test.

Results

Success of ablation

According to the criteria used in this study, ablation was successful in 110 out of 180 patients (61%) (Fig. 1). Median follow-up time was 55 months. Twelve patients died of thyroid cancer, of which four had died within 1 year of initial treatment. Sixteen patients had recurrence of thyroid cancer. Twenty-nine patients never became free of the disease during follow-up, including six out of the eight patients who died. Seven of those 29 patients

Figure 1 Status of patients, 1 year after administration of the ablative dosage of I-131. die: to die of differentiated thyroid carcinoma before the end of follow-up.

had a short follow-up of less than 4 years, so they may not have received the maximum treatment yet. Two patients died of recurrent disease.

Survival analyses

Of the patients with successful ablation, 87% (S.E. 4.8%) were still free of the disease 10 years later. Of the patients with unsuccessful ablation who eventually did become free of disease, only 50% (S.E. 14%) were still free of the disease after 10 years (Fig. 2). The difference between the two Kaplan–Meier curves was significant (log rank = 11.1, $P < 0.001$). At 5 years, disease-free survival was 93% versus 62%.

In patients who were alive at the 1-year follow-up, those with successful ablation had a thyroid-cancer-specific survival of 100% for the 5 years after ablation and 95% (S.E. 4.1%) for the 10 years after ablation, whereas patients with unsuccessful ablation had a thyroid cancer-specific survival of 89% (S.E. 4.0%) for the 5 years after ablation and 78% (S.E. 8.3%) for the 10 years after ablation (Fig. 3). The difference between these two survival curves was also statistically significant (log rank = 7.16; $P = 0.007$).

We analysed factors at the time of ablation that might influence the outcome of the first dosage of I-131. Results of these analyses are displayed in Table 2. Patients with a higher serum Tg level at the time of ablation ($P < 0.001$), patients with lymph-node metastasis discovered pre- or perioperatively ($P = 0.04$) and patients with distant metastasis ($P < 0.001$) turned out to have less chance of achieving successful ablation with the initial dosage of I-131.

Discussion

Our study shows that the success of ablation is a prognostic factor for disease-free interval and survival in

Figure 2 Kaplan–Meier plot of the duration of the disease-free interval in patients with successful and those with unsuccessful ablation.

Figure 3 Kaplan–Meier plot of the thyroid-cancer-specific survival in patients with successful and those with unsuccessful ablation.

differentiated thyroid cancer patients. Unsuccessful ablation carries with it a considerably higher risk of recurrence; more importantly, it is not even certain that a patient can be made free of detectable disease. Our results support previous studies on the beneficial effects of radioiodine ablation for prognosis of patients with differentiated thyroid cancer (2, 5, 20). In these studies, however, success of ablation as determined by Tg levels and scintigraphy was not reported as a prognostic factor. Some factors can influence the success of ablation. These factors include Tg levels at time of ablation, presence of pathological lymph nodes and distant metastasis. Since Tg is produced by normal or neoplastic thyrocytes, one can assume that higher Tg levels indicate a larger mass of functioning thyroid cells. Therefore, the chance of successful ablation is determined by the mass of normal and neoplastic thyroid tissue remaining after surgery. What could be of further importance is the grade of differentiation of the thyroid cancer cells. In some patients, the carcinoma de-differentiates in the course of the disease (21, 22). One of the mechanisms affected by this de-differentiation is the sodium-iodine symporter, which is essential for the uptake of I-131 by thyroid cancer cells. Cells that do not take up I-131 are much more likely to be persistent, but cannot be seen or measured scintigraphically. It is

Table 2 P values of factors influencing success of ablation.

Possible prognostic variable	P
Age	0.09
TSH levels	0.19
Total thyroxine levels	0.17
Tg levels	<0.001
Sex	0.07
Papillary/follicular carcinoma	1.00
Tumour diameter	0.15
Nodular metastasis	0.04
Distant metastasis	<0.001

therefore impossible to say how much our results are influenced by this phenomenon.

Finding that a patient has an unsuccessful ablation adversely affects prognosis: a considerable number of patients in whom initial ablation was unsuccessful will never, or only after a number of additional therapeutic dosages of I-131, become free of detectable disease. Furthermore, even if they eventually do become free of disease, there is an increased chance that the thyroid cancer will return sooner or later.

Lymph-node or distant metastasis is a well-known adverse prognostic variable for thyroid cancer (2, 3, 23–26). Surprising, however, the age at the time of ablation had no statistically significant influence on the outcome of the first dosage of I-131 in our study population. Normally, age is considered to be one of the more important prognostic factors in thyroid cancer.

Several studies have reported that high Tg levels at the time of ablation can be related to initial metastasis or recurrence (27–32). Muratet *et al.* (13) also found a significant relationship between Tg levels and the chance of successful ablation. Interestingly, they observed that a rise in Tg levels shortly after administration of I-131 is correlated with a lower chance of successful ablation. A similar report came from the group of Baudin *et al.* (32), who reported that the slope of rise or fall of Tg levels measured in high TSH conditions, compared with Tg levels at the time of ablation, had the higher value for prediction of recurrences.

Further research into the significance of Tg levels at the time of ablation seems warranted, especially with regard to the success of ablation. This could possibly lead to improved dosage schemes for individual patients. In that area, it would be interesting to conduct further research into the significance of measuring Tg levels after the ablative dosage: what is the earliest moment that they need to be undetectable during TSH stimulation, if there is to be a chance of achieving complete ablation? This could possibly lead to earlier additional therapy. In order to answer this question, we may want to turn to I-131 therapy for benign conditions. In patients treated for benign thyroid diseases, no further effect of I-131 therapy can be measured from 3 months after administration onward (33–35). This is considered to be so, even though 3 months after ablation would be much earlier than recent recommendations of 6–12 months (36). Perhaps that would be a good point in time for post-ablation follow-up, instead of the current follow-up at 1 year. This means that any thyroid cancer cell not killed in the first blast will have 9 months less to proliferate and spread.

Unsuccessful ablation is an adverse event in the follow-up of differentiated thyroid carcinoma. Patients in whom this is found should be followed much more intensively than patients in whom ablation was successful: they may never become free of disease, and even if they do, there is a high risk of recurrence.

Therefore, it seems important to treat thyroid cancer as early and as intensively as possible, in order to achieve the best possible prognosis for patients.

In conclusion, unsuccessful ablation dramatically lowers the prognosis of disease-free survival in patients; they should be followed much more intensively than those in whom ablation was successful with one dosage. The extent of the remaining normal or neoplastic thyroid tissue contributes to a higher risk of unsuccessful ablation after the first dosage of I-131 for the treatment of thyroid cancer.

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Received 21 July 2004

Accepted 5 October 2004