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Feasibility of a randomized trial on adjuvant radio-iodine therapy in differentiated thyroid cancer

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Summary

BACKGROUND Justification for adjuvant radio-iodine (I-131) therapy in differentiated thyroid cancer (DTC) is purely based on retrospective data. This is true for ablative therapy and even more so for high-dosage adjuvant schedules. Randomized trials on the latter application are considered impossible due to anticipated formidable sample sizes required in a disease with an overall excellent prognosis like DTC.

OBJECTIVE To develop and validate a model that could stratify for risk of recurrence, rather than survival, as is usually done in prognostic indices, and secondly, to use this model to estimate the sample size required for a randomized trial.

DESIGN, PATIENTS AND RESULTS From databases of three large Dutch centres, we identified 342 consecutive patients without known residual DTC after (near-) total thyroidectomy. Using Cox proportional hazards analysis, a model was validated that clearly distinguished risk categories of recurrence using commonly available baseline variables. The model included age, N stage at presentation and T stage in papillary carcinoma. According to this stratification, a subset of patients at substantial risk for relapse (30–40%) was

identified. They could be eligible for a trial assessing the impact of high-dose adjuvant I-131 on recurrence rates. Assuming a clinically relevant effect of 30% reduction of relapses, 290 patients would have to be entered in either arm (α 0.05, power 80%).

CONCLUSION We conclude that even though a randomized trial on this issue will be difficult to design and conduct, sample size is not the main problem.

About 40 years after the introduction of radio-iodine (I-131) therapy in differentiated thyroid cancer (DTC; Beierwaltes *et al.*, 1982), its exact role in the management of these patients is still debated. Ablative therapy (using, e.g. 1.85 GBq or 50 mCi) I-131 destroys the functional thyroid remnant and improves the specificity of serum thyroglobulin measurements during follow-up. It has also been suggested that much higher I-131 doses are more effective to eradicate subclinical residual tumour tissue, i.e. after apparently radical surgery of the primary tumour. In that case, much higher dosages (at least 5.55 GBq or 150 mCi) are given provided that the functional postoperative thyroid remnant is small. Larger remnants require ablative therapy first, followed by the higher dose after several months.

It is unclear whether such adjuvant high-dosage I-131 therapy, i.e. intended to eradicate residual tumour tissue in radically operated patients, effectively reduces recurrence rates or mortality, or both (Beierwaltes, 1987; Hay *et al.*, 1993; Mazzaferri & Jhiang, 1994; McDougall, 1997). Radiobiological and retrospective data provide insufficient evidence. Although preferable, randomized trials are considered impracticable due to the anticipated formidable study sample (Wong *et al.*, 1990; McDougall, 1997). This is obviously correct if the primary outcome measure is survival of the total population of thyroid cancer patients. However, because apparently localized DTC carries an excellent prognosis *quoad vitam*, a more relevant endpoint might be the relapse rate or relapse-free survival. In the past decades, several prognostic indices (Byar *et al.*, 1979; Tubiana *et al.*, 1985; Cady & Rossi, 1988; Mazzaferri, 1991; Davis *et al.*, 1995; Schlumberger & Pacini, 1999) have been proposed but most comprise patients with non-radically operated primary tumours or distant metastases with stratification by survival, not relapse-free interval.

The aim of the present study was to develop and validate a model for stratification of these patients with respect to their risk of relapse within a relevant time frame, in order to assess the

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sample size needed for a randomized evaluation of the impact of high-dosage adjuvant I-131 therapy.

Methods

We analysed the medical records of DTC patients, referred between 1975 and 1995 to three Dutch hospitals (one university and two community), using the files of the Department of Nuclear Medicine of the VUmc Amsterdam (nuclear medicine, pathology), of the Departments of Radiotherapy and Nuclear Medicine of the Dr Bernard Verbeeten Institute Tilburg (BVI) and the Catharina Hospital, Eindhoven (CHE). Besides patients of their own centres, these institutes serve many community hospitals.

Inclusion criteria were: papillary or follicular thyroid carcinoma without known residual disease after (near-)total thyroidectomy, and no known distant metastases at presentation (after thyroidectomy and initial I-131 scan, if available). Twelve per cent of these patients were diagnosed prior to 1980, and 50% between 1981 and 1990.

From these records, we extracted data on patient characteristics (age, gender, duration of follow-up, recurrence, mortality), tumour profiles (histological type, diameter, lymph node involvement, local invasiveness), therapy (extent of surgery, completeness of resection, I-131 ablation or therapy) and follow-up (duration, recurrence-free interval, mortality). Data on pathology, surgery and follow-up were obtained from referring hospitals. For the purpose of this analysis, clinically established recurrence was at endpoint. We considered a patient to be free of disease if the thyroglobulin (typically during thyroid hormone suppression) was not measurable and if there was no clinical evidence of disease. Follow-up data were registered from the date of postoperative I-131 or that of thyroidectomy in case no I-131 had been given, until recurrence, death or final clinical follow-up in alive patients without relapse.

Statistical analysis

The prognostic factors were investigated using stepwise survival analyses with Cox proportional hazards model (BMDP software, BMDP Statistical Software Inc., Los Angeles, USA). The direction of the search was forward; the selection of next variables was based on the likelihood computation. For model building, a random sample of about 50% of the population was used; the data of the remaining patients (test set) were used for validation purposes. Survival curves were estimated using the Kaplan–Meier method.

Results

In the 20-year period, 342 patients were identified who had differentiated papillary or follicular thyroid carcinoma, who had been radically operated upon and who had no known residual disease after (near-)total thyroidectomy and (in 90%) followed

by scintigraphy performed between 3 and 7 days after I-131 therapy. In one of the three institutions, preablative diagnostic scintigraphy was done with 37 MBq I-131. Stunning is unlikely to be important at such dosage (Cholewinski *et al.*, 2000). Doses of postoperative I-131 ranged from 740 to 5550 MBq. Patient characteristics are summarised in Table 1. Mean follow-up duration in the patients without recurrence or death was 129 months; 80% had a follow-up of at least 6 years. Fourteen per cent of these

Table 1 Demography and clinical data of the eligible patients (*n* = 342)

		% of total (<i>n</i> = 342)
Female (<i>n</i>)	266	77.8
Papillary carcinoma (<i>n</i>)	230	67.3
Age at presentation (years; mean ± SD)	44.6 ± 15.6	
T stage (<i>n</i>)		
pT 1	51	14.9
pT 2	179	52.3
pT 3	51	14.9
pT 4	48	14.0
Unknown	13	3.8
N stage (<i>n</i>)		
p ¹³¹ I N0	251	73.4
p ¹³¹ I N1	91	26.6
AMES (<i>n</i>)		
Low	250	73.1
High	75	21.9
Unknown	17	5
MACIS (<i>n</i>)		
5–5.9	201	58.8
6–6.9	80	23.4
7–7.9	27	7.9
≥ 8	12	3.5
Unknown	22	6.4
Postoperative I-131 (<i>n</i>)	308	90
Ablation	241*	
Therapy (≥ 5550 MBq)	67	
Hospital (<i>n</i>)		
VUmc	94	27.5
BVI	150	43.9
CHE	98	28.7
Follow-up, months; median (IQR)		
No relapse	118.5 (79.4–167.9)	
Relapse†	31.7 (17.6–86.8)	
Death, no relapse	49.9 (27.0–82.7)	
Relapse (<i>n</i>)	48	14
Local relapse	19	
Metastases	17	
Local and metastases	12	

IQR, interquartile range. *Nine patients 740 MBq. †Time to relapse.

patients ($n = 48$) presented with recurrent disease during follow-up, 80% within 7 years after initial presentation. Sixty per cent of the patients who had a relapse died within the observation period vs. 8% of the patients without recurrent disease.

Model building, validation and application

For model building purposes, a learning set was randomly drawn consisting of 53% of the study population. Table 2 shows that randomization provided reasonably well-balanced groups. Tested parameters included: gender, histological type, age, pT stage, p/¹³¹I N stage (after surgery, and high-dosage I-131 scanning, if applicable), stage according to the Age, Metastases to distant sites, Extent of the primary tumour, Size larger than 5 cm (AMES) (Cady *et al.*, 1988), Metastasis, Age, Completeness of resection, Invasion, Size (MACIS) (Hay *et al.*, 1993) and Mazzaferri (1991) classifications, I-131 therapy and hospital. Even though the AMES and MACIS indices were developed for papillary cancers, we tested their prognostic value in the model, reasoning that the use of existing indices would be preferable over developing yet another index.

Table 2 Characteristics of the two random samples to build (learning set) and validate (test set) the model

	Learning set	Test set
Patients (n)	180	162
Age (years, mean $\pm$ SD)	44.7 $\pm$ 15.6	44.4 $\pm$ 15.6
Female	141 (78.3%)	125 (77.2%)
Papillary	122 (67.8%)	108 (66.7%)
AMES: high risk	34 (18.9%)	41 (25.3%)
T stage		
pT1,2	124 (68.9%)	106 (65.4%)
pT3,4	49	50
Unknown	7	6
N stage		
p/ ¹³¹ I N1	46 (25.6%)	45 (27.8%)
Postoperative I-131 (n)		
Ablation	130 (72.2%)	111 (68.5%)
Therapy ($\geq$ 5550 MBq)	36	31
Hospital		
VUmc	45	49
BVI	81 (45%)	69 (42.6%)
CHE	54 (30%)	44 (27.2%)
Relapse	26 (14.4%)	22 (13.6%)
Mortality	8	11
Follow-up, months; median (IQR)		
Relapse*	36.1 (22.5–91.8)	30.5 (15.5–81.5)
Death	48.6 (28.4–65.4)	71 (27–105.1)
No event	117.3 (82.9–174.7)	120.7 (74.8–160.4)

IQR, interquartile range. *Time to relapse.

Table 3 Model built with multivariate analysis of prognostic factors with Cox regression analysis in the learning set ($n = 180$)

Variable	To be entered in the model as:	Coefficient	SE	P-value
Age	years/20	1.0544	0.2861	0.0001
N stage	0 or 1	0.8826	0.4336	0.04
T3,4 papillary cancer	0 or 1	1.0999	0.4528	0.01

Multivariate Cox regression analysis identified three significant variables predictive of relapse: age, the N stage and, for papillary carcinoma, the T stage (Table 3). In this sample, there did not seem to be an effect of the hospital or the administration of I-131 (typically ablation). Randomization proved to have been successful to the extent that no significant differences were found between the two sets, with respect to the items listed in Table 2.

For validation, the model was applied to the test set, and again Cox regressions were done. When the model was entered as the first parameter, none of the other model components, or any other tested variable, proved to have a significant impact (age: $P = 0.30$, postoperative N stage: $P = 0.98$, papillary T3/4: $P = 0.17$), as was also true for any of the other tested variables. It may therefore be concluded that the model has been validated.

After validation, we pooled the two datasets to obtain a more powerful estimate of the threshold defining the high-risk category. When using the model with a cut-off value of 3 (established by comparison of multiple Kaplan–Meier analyses using different thresholds), which was found to have the best operating characteristics, a subgroup of 36% of the population was identified as having a 30–40% risk of recurrence within 10 years after presentation (Fig. 1). Hence, assuming a clinically relevant effect of 30% reduction of relapses within that time frame (from 30 to 20%), 290 patients would have to be entered in either arm (α 0.05, power 80%), or 120 if 50% reduction of risk is anticipated.

Discussion

Using data from a population consisting of apparently localized thyroid cancer treated with (near-)total thyroidectomy, we identified a subset of patients at such risk of relapse that they would be eligible for a randomized trial evaluating the effect of adjuvant I-131 therapy.

Compared to most other solid tumours, differentiated papillary and follicular thyroid cancer carries a favourable prognosis. Early diagnosis and effective surgery, the low proliferative activity and the possibility to suppress the growth-stimulating hormone TSH largely contribute to this. Whereas the efficacy of radio-iodine therapy in the management of small, clinically manifest metastases is beyond discussion (Beierwaltes *et al.*, 1982), its impact

Fig. 1 Time to recurrence using a threshold of 3 obtained from the model ($n = 342$, log rank test, $P < 0.001$). Dashed and straight curves represent patients with model value ≥ 3 and < 3 , respectively.

in the adjuvant setting is controversial. Proponents of post-operative high-dose (e.g. 5550 MBq I-131) radio-iodine therapy consider this dose to be adjuvant radiation therapy to eradicate occult metastases not detected by I-131 imaging (Beierwaltes, 1987). Proof of such effect can only be assumed on retrospective data. From a biological perspective (absent vascularization of micrometastases with a diameter < 4 mm; Jain, 1991) and from microdosimetric considerations (Wheldon *et al.*, 1991; Sautter-Bihl *et al.*, 1992), the hypothesis that I-131 kills microscopic metastases is not convincing. In effect, the TSH pulses associated with I-131 therapy may also stimulate tumour growth.

Of the prognostic models published so far, several have addressed relapse rate besides mortality. Often, the datasets do not apply to the eligibility criteria for a trial on high-dose adjuvant therapy. The study by Tubiana *et al.* (1985) also focussed on relapse rates but their data set comprised only 19% of patients after total thyroidectomy and included non-radically operated patients, who should not be eligible for an trial on the effect of I-131 in the adjuvant setting. On the other hand, their follow-up was clearly more extended than in our patients. Even though relapses can occur very late after initial diagnosis, it is also known that the annual relapse rate in patients with apparently localized disease rapidly declines during the first 5 years after initial presentation (Tubiana *et al.*, 1985; Wong *et al.*, 1990). With a mean follow-up of 10 years and 70% of event-free population followed for at least 7 years, we estimate that most recurrences must have been identified. With respect to the applicability of the data to the entire thyroid cancer population, it could be argued that our database might contain only a limited proportion of the eligible DTC population. To determine the proportion of DTC patients referred to these institutions, we have compared our

records with the available data of the database of the Comprehensive Cancer Center South. This is a comprehensive registration of cancer patients, and includes data on TNM stage and I-131 referrals. It was found that about 60% of the DTC patients in the geographical area of CHE and BVI are referred for I-131, with a clear preference for higher TNM stages (Kuijpers *et al.*, 2002). We therefore assume that most patients who would have been eligible for a trial on the adjuvant effect of I-131 were included in our study. As expected, the number of follicular cancers within this time frame was relatively small. Even though the sample was representative, our study may therefore have lacked the statistical power to recognize prognostic relevance of the histological subtype.

We considered a 30% relative reduction of relapse risk as clinically relevant. However, the anticipated efficacy of radio-iodine in reducing thyroid cancer relapse rate has been suggested to be over 50% (Wong *et al.*, 1990). In our sample, most patients were treated with ablative doses of I-131. Accordingly, this risk profile would be most suited as a baseline for a trial comparing ablative and high doses of I-131. If ablation itself has any effect on relapse rates, our estimation of the relapse rate is rather conservative. Therefore, our assumptions underlying the sample size estimation appear to be realistic.

In summary, the generally held opinion that randomized trials on the usefulness of adjuvant radio-iodine therapy in patients with differentiated follicular or papillary cancer are not feasible because of nonrealistic sample sizes is refuted. The design and conduct of such randomized trials may encounter many difficulties but sample size should not be one of them. Indeed, if a multicentre trial had started in the early 1980s when the adjuvant concept was proposed, the results would have benefited today's patients.

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