JOURNAL OF INSURANCE MEDICINE

J Insur Med 2001;33:133–137

ORIGINAL ARTICLE

Long-Term Comparative Mortality in Hyperthyroid Patients Treated with Radio-Iodine, a Cohort Study in England

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Mortality Abstract 058-M2 (cross refer 723-M2)

Background.—The focus of this long-term study (entry 1950–1989, follow-up to 1996) on hyperthyroid patients treated with ^{131}I was on all-cause mortality and some specific causes other than cancer. The study was carried out on 7209 patients who were residents of the Midlands area around Birmingham, England. In a total exposure of 105,028 patient-years, 3611 deaths were observed, compared with 3186 deaths expected from age/sex-matched rates in the English life tables.

Results.—Data were reported for observed and expected deaths, and SMR values (standardized mortality ratios to one decimal place) by selected causes of death in combinations with duration, age, and 3 dosage groups of ^{131}I. Exposure data were given only for the dosage groups of ^{131}I, not for the results by age or duration.

Conclusions.—Comparative mortality was significantly increased for all-cause mortality (but with an SMR of only 1.13), and also for cardiovascular and cerebrovascular deaths, and deaths from fracture. Excess mortality was greatest in the first year after entry, and decreased thereafter. There was no reported increase in cancer mortality.

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Key words: Comparative mortality, mortality by cause, hyperthyroidism, radio-iodine, follow-up study (long-term).

Received: December 4, 2000.

Accepted: January 8, 2001.

References

1. Franklyn JA, Maisonneuve P, Sheppard MC, et al. Mortality after the treatment of hyperthyroidism with radioactive iodine. *N Engl J Med.* 1998;338:712–718.
2. Singer RB. Long-term comparative cancer mortality after use of radio-iodine in the treatment of hyperthyroidism, a fully reported multicenter study (Mortality Article 058-M1). *J Insur Med.* 2001;33:138–142.
3. *1983 Medical Impairment Study.* Compiled and Published by the Society of Actuaries and the Association of Life Insurance Medical Directors of America (1984). See category U5, Hyperthyroidism, pp. 30 and 98.

OBJECTIVE

The objective of this Abstract is to present selected results of comparative mortality in the very long-term follow-up (FU) study of hyperthyroid patients near Birmingham, England, treated with ^{131}I. In addition to all-cause mortality, the authors presented results on mortality by specific cardiovascular and other causes in which excess mortality was found (no excess in cancer).

SUBJECTS STUDIED

Data were collected in the Birmingham (England) Thyroid Follow-up Register on pa-

Table 1. Characteristics of 7209 Hyperthyroid Patients Treated with ^{131}I, 1950–1989, in the Birmingham (England) Thyroid Follow-up Register*

Characteristic	All Patients	Cumulative Dose of ^{131}I (MBq)		
		<221	221-480	>480
Number of patients	7209	3440	2559	1194
Exposure, (patient-years)	105,028	48,037	39,947	16,853
Mean follow-up duration (years)	14.6	14.0	15.6	14.1
Female percentage of total	83	86	83	84
Mean age (years)	57	56	58	58

* Adapted from Table 1 of Franklyn et al.[1]

tients with hyperthyroidism who were treated with ^{131}I during the period 1950–1989. The initial cohort list of 7772 patients was sent to the National Health Service Register. After checking, 563 patients were eliminated because of missing data or other technical reasons, leaving a cohort of 7209 patients for FU. The mean age was 57 years, with a range from 14 to 94 years, and the proportion of females was 83% (Table 1). The average dose of ^{131}I was 314 MBq (Bq is the abbreviation for a unit of radioactive dosage, the Becquerel). As shown in Table 1, the patients were subdivided into 3 dosage groups: <221, 221–480, and >480 MBq, with exposure data for each group and the total cohort. In most patients, the ^{131}I was given as a single dose, but the dosage used for classification was the cumulative dose. Data for age/sex distribution were not given in the article, but must have been used to derive expected deaths from the mortality rates in the English Life Tables. National tables were used in preference to the less-detailed regional tables for the Midlands area.

FOLLOW-UP

The vital status of the 7209 patients was determined on March 1, 1996, through the death register of the Office of National Statistics. Death certificates were obtained for the 3611 patients whose deaths were recorded (patients not listed in the Registry of the National Health Service had been excluded).

RESULTS

Table 2 provides precise results of comparative mortality for durations 1 year and up, and for all durations, but only an approximation for duration 0–1 year, because no exposure data are available for the duration periods 0–1, 1–10 and 10–20 years, and 20 years up, in Table 3 of the source article. I have assumed an approximate exposure, E, of 7209 for the first year, probably an overestimate, since it is likely that at least a few patients were lost to the FU in the first year (no patients came to the end of the FU because all patients had a potential complete FU from 1990 to March 1, 1996). For duration 0–1 year, 219 total deaths were observed, and smaller numbers for the specific causes of death listed in the table. With 128.0 expected deaths, the mortality ratio (MR) was 181%, a highly significant increase, and the excess death rate (EDR) was 13.6 extra deaths per 1000 per year. If E is too large, the mortality rate, q, and the EDR are overestimated. However, in all probability, the errors produced by this approximation of E are relatively small, and there would be no error in the MR. Since E in the first year is so small relative to the total E over such a long period of FU, the error in E for durations 1 year and up is trivial. The E value for 0–1 year is therefore the only one enclosed in parentheses to indicate the approximation. There is no error in the tabular rate results for all durations.

In Table 2, I have obtained the data for "All

Table 2. Comparative Mortality by Duration and Cause of Death, Hyperthyroid Patients Treated with ^{131}I, in the Birmingham (England) Thyroid Follow-up Register, 1950–1989

Cause of Death	Exposure (patient-years) E	Number of Deaths Observed d	Number of Deaths Expected* d′	Mortality Ratio 100d/d′	Mean Annual Mortality Rate/1000 Observed q	Mean Annual Mortality Rate/1000 Expected q′	Mean Annual Mortality Rate/1000 Excess (q − q′)
0–1 year duration, 7209 patients							
Endocrine and metabolic	(7209)†	39	1.7	2200%‡	5.4	0.2	5.2
All cardiovascular	(7209)	63	37.7	162‡	8.5	5.2	3.3
Cerebrovascular	(7209)	33	14.7	220‡	4.6	2.1	2.5
Fractures	(7209)	2	1.0	200NS	0.3	0.1	0.2
All other	(7209)	84	65.7	128‡	11.7	9.1	2.6
All causes	(7209)	219	128.0	181‡	30.4	16.8	13.6
Duration 1 year up, 6990 patients							
Endocrine and metabolic	97,819	120	49	245%‡	1.2	0.5	0.7
All cardiovascular	97,819	1894	1539	123‡	19.4	15.7	3.7
Cerebrovascular	97,819	572	431	133‡	5.8	4.4	1.4
Fractures	97,819	48	27	192‡	0.5	0.3	0.2
All other	97,819	758	1019	74‡	7.8	10.4	−2.6
All causes	97,819	3392	3065	111‡	34.7	31.3	3.4
All durations, 7209 patients							
Endocrine and metabolic	105,028	159	51	310%‡	1.5	0.5	1.0
All cardiovascular	105,028	1955	1577	129‡	18.6	15.0	3.6
Cerebrovascular	105,028	605	446	136*	5.8	4.2	1.6
Fractures	105,028	50	28	192‡	0.5	0.2	0.3
All other	105,028	842	1084	78‡	8.0	10.3	−2.3
All causes	105,028	3611	3186	113‡	34.4	30.3	4.1

* Basis of expected deaths: mortality rates in contemporary English Life Tables.

† E for first year probably overestimated as equal to 7209 entrants (total E is precise). See text.

‡ Difference in mortality ratio from 100% significant at 95% confidence level. NS = not significant.

Other Causes" as the difference between the numbers of total observed and expected deaths, and the respective sums for deaths by the specific causes listed. These data are not shown in the tables of the source article, although in the text it is stated that deaths for cancer, respiratory, digestive, and genito-urinary tracts were not elevated. This is indeed true after the first year, for which the MR in Table 2 was only 74%, a significant deficit in mortality for all other causes not listed specifically. Deaths due to "Endocrine and Metabolic" causes (mostly due to hyperthyroidism) were especially high in the first year, with an MR of 1200%. The EDR of 5.2 per 1000 is unusually high for a cause of death of such low prevalence (cause-specific q′ of only 0.2 per 1000). After 1 year, the MR dropped to 245%, and overall it was 310%. However, the overall total MR was only 113%, reflecting excess mortality in cardiovascular and other specific causes, but an MR of under 80% for cancer and all other causes. The overall EDR of 4.1 per 1000 was based on an overall aggregate mean q of about 34 per 1000 and expected mean q′ of about 30 per 1000, reflecting a mean attained age much higher than the mean entry age of 57 years.

The authors of the source article emphasize the excess mortality found in the cardiovascular diseases, cerebrovascular diseases at most durations, and in fractures after the 10th year. Data were given for the specific cardiovascular diseases of rheumatic, hypertensive, and ischemic heart disease, and diseases of the pulmonary circulation and other heart diseases (not shown in Table 2). For the most part, the SMR values were significantly

Table 3. Comparative Mortality by Cause of Death and Dosage Level of ^{131}I Used in Treatment of Hyperthyroid Patients in the Birmingham (England) Thyroid Follow-up Register

Cause of Death	Exposure (patient-years) E	Number of Deaths		Mortality Ratio 100d/d′	Mean Annual Mortality Rate/1000		
		Observed d	Expected* d′		Observed q	Expected q′	Excess (q − q′)
Low dose ^{131}I (<221 MBq)							
Endocrine and metabolic	48,057	49	21	235%†	1.0	0.4	0.6
All cardiovascular	48,057	492	402	122†	9.2	8.4	0.8
Cerebrovascular	48,057	207	172	120†	4.7	3.0	1.7
All other	48,057	626	670	93NS	13.0	13.9	−0.9
All causes	48,057	1324	1265	105NS	27.5	26.3	1.2
Intermediate dose ^{131}I (221–480 MBq)							
Endocrine and metabolic	39,947	73	20	365%†	1.8	0.5	1.3
All cardiovascular	39,947	575	423	122†	12.9	10.6	2.3
Cerebrovascular	39,947	268	188	143†	6.7	4.7	2.0
All other	39,947	643	686	94NS	16.1	17.2	−1.1
All causes	39,947	1496	1317	114†	37.4	33.0	4.4
High dose ^{131}I (>480 MBq)							
Endocrine and metabolic	16,853	37	8.8	420%†	2.2	0.5	1.7
All cardiovascular	16,853	299	197	157†	17.7	11.3	6.4
Cerebrovascular	16,853	129	86	150†	7.7	5.1	2.6
All other	16,853	310	312	99NS	18.4	18.5	−0.1
All causes	16,853	775	598	130†	46.0	35.5	10.5

* Basis of expected deaths: mortality rates in contemporary English Life Tables.

† Difference in mortality ratio from 100% significant at 95% confidence level. NS = not significant.

elevated at all durations under 20 years, but the elevation was marginal after 20 years. As shown in Table 2, the SMR values were significantly elevated before and after 1 year of duration for all specific causes of death, except for fractures under 1 year.

Table 3 shows comparative mortality, all ages and durations combined, by dosage level of ^{131}I, for all causes of deaths shown in Table 2, except for fractures. Excess mortality was present in most categories shown, except that MR was consistently under 100% for "All Other Causes." The MR values tended to increase with dosage level, and most elevated MR values were statistically significant at the 95% confidence level, except for the overall MR of 105% at the lowest dosage level. The trend for total mortality to increase by dosage level was significant ($P < .001$). The difference in mortality is also clearly shown in the distinctly separated Kaplan-Meier survival graphs for the three dosage levels, duration 0–42 years, in Figure 1 of the source article.[1] As in Table 2, the highest MR values were found for endocrine and metabolic diseases (which included hyperthyroidism); these ranged from 235 to 420% in ascending order of dosage level. The authors of the source article attributed the increase by dosage level in mortality due to hyperthyroidism and cardiovascular diseases to the likelihood of use of higher doses of ^{131}I in more severe cases, and in cases with more severe complications, including atrial fibrillation.

COMMENT

As noted in the companion Abstract[2] on cancer mortality after treatment of hyperthyroid patients with ^{131}I, exposure is identical for any set of mortality data by cause of death. Observed and expected deaths are additive to the totals, all causes combined, but cause-specific MR values may vary over a

wide range, and they cannot be averaged without reference to the weighting of the distribution of deaths. On the other hand, mortality rates, q, q′, and EDR are all additive to the totals for all causes combined. All of the above can be confirmed by a careful inspection of the data in Tables 2 and 3.

One important difference between the two Abstracts is the provision of exposure data in the current Abstract that permits the calculation of comparative mortality for all causes combined, the crucial item of comparative mortality needed by the medical director or underwriter. The overall MR in this English study was 181% at 0–1 year of duration, but only 111% thereafter. This MR is based on population expected rates. What would the MR have been if the study had been conducted on life insurance applicants in the US? Any approximation of this must be a crude one because of the extremely long average duration of FU. The cohort was 83% female, so I have used the 1981 female English Life Table female rates to estimate the attained age corresponding to an aggregate mean expected rate of 30 per 1000 per year (last line of Table 2). This estimated age is 72 years. If we enter the 1975–80 Ultimate Table for females age 72, the q′ value is 21 per 1000. Then, if we add the EDR we get 21 + 4 = 25 for an estimated "observed" aggregate rate for an insured US cohort. The MR is 25/21 = 119%. This is still within the standard limits, if we exclude the less-favorable experience at duration 0–1 year.

It is evident that studies of comparative mortality by cause of death have their intrinsic interest, but are of limited value in mortality risk appraisal if they do not provide results on total mortality, which was the case with the larger cancer mortality study.[2] In the current long-term study, we have seen that the MR, all durations combined, is probably lower than the customary standard limit of 125%. My opinion is that most cases of hyperthyroidism successfully treated with ^{131}I are eligible for standard insurance if they are free of other ratable risk factors. This opinion is reinforced by the results for hyperthyroidism as a single impairment in the *1983 Medical Impairment Study.*[3] The results for the unusually large female experience reflected lack of success in underwriting: the MR was 135% (98 deaths) for the standard issues, but only 89% (46 deaths) for the substandard issues. If we combine the standard and substandard issues, the total exposure of over 35,000 policy-years yielded an MR of 117%, with 139 observed and 119 expected deaths. The male experience was consistently good, with an MR of 91% for standard issues and 90% for substandard issues (92 and 35 deaths, respectively). I believe that for underwriting hyperthyroidism as a single impairment we should rely on these results and issue a standard policy if there are no other ratable factors. Most patients in the US have been managed with ^{131}I as the standard method of treatment since about 1950.[2] Adverse effects of the use of a radioactive substance appear to be minimal in these two very long-term studies.[1,2]