Clinical outcome and costs of care in radioiodine treatment of hyperthyroidism

C. A. HARDISTY, MD, FRCP, *Consultant Physician, Northern General Hospital, Sheffield*
S. J. JONES, MPhil, *Lecturer in General Practice, University of Nottingham*
A. J. HEDLEY, MD, FRCP, *Professor of Public Health, University of Glasgow*
D. S. MUNRO, MD, FRCP, *Professor of Medicine, University of Sheffield and Northern General Hospital*
P. D. BEWSHER, MD, FRCP(Ed), *Reader in Medicine and Therapeutics, University of Aberdeen*
R. D. WEIR*, MD, FRCP, *Professor of Community Medicine, University of Aberdeen*

*Chairman SAFUR Steering Group: Other members of the group include — Dundee: Dr R. J. Jung; Edinburgh: Professor C. R. W. Edwards; Glasgow: Dr W. D. Alexander, Dr R. E. Young; Inverness: Dr J. A. Burton

ABSTRACT – The long-term clinical outcome and costs of treatment of hyperthyroidism with radioiodine have been examined in two cohorts of patients from Sheffield and Scotland. The majority of patients in both series were considered to have Graves' disease. The Sheffield patients (660) were included in a trial of three radioiodine dose regimens of 3,500 (312), 7,000 (323) and 14,000 (25) rad determined using a formula for accurate dosimetry. The Scottish patients (3,920) drawn from five centres in Aberdeen, Dundee, Edinburgh, Glasgow and Inverness were treated using an arbitrary scale, for the activity of radioiodine administered, related to goitre size. Their results are grouped into five MBq 'dose' bands: 37–185, 186–370, 371–555, 556–740 and 741+. The proportion of patients with persistent hyperthyroidism was higher in both cohorts for low-dose radioiodine regimens, but 15–25% of patients who received high doses showed persistent hyperthyroidism. Early and late onset hypothyroidism was lower after low doses but differences between the treatment groups were small in terms of clinical benefit. Total morbidity at 10 years follow-up, in terms of hyperthyroidism, and hypothyroidism, was highest after low-dose therapy. There was little variation in total costs, but patient costs were lowest for the Scottish regimen and highest for low-dose therapy. A dose of at least 370–555 MBq which will ensure early elimination of hyperthyroidism will also limit the medical workload and total costs.

Radioiodine has been used for the treatment of hyperthyroidism for more than 40 years [1] and many studies have been carried out to assess the long-term clinical outcome. Some patients are at risk of persistent hyperthyroidism or rarely of recurrent hyperthyroidism if insufficient radioiodine is given. All patients may remain at risk of developing hypothyroidism during their lifetime whatever the initial dosage used [2–4]. The possibility of avoiding these complications has been explored in several centres but it was argued many years ago that hypothyroidism was inevitable in varying proportions of patients, despite attempts at precision dosimetry [5, 6], the use of low doses [7, 8], different isotopes [9, 10] or other therapeutic variations.

There are very wide variations in current practice. In one centre, 'ablative' doses (555 MBq) are advocated as a method of achieving an early remission, linked to effective follow-up to ensure adequate supervision and treatment of hypothyroidism [11]. These authors advocated follow-up of patients at an outpatient clinic until hypothyroidism developed; in their study, 64% were hypothyroid at 1 year, but in other centres between 60% and 70% of patients treated in this way remained euthyroid for 2 years or much longer [12]. In contrast, other groups have continued to favour low-dose therapy repeated, if necessary, at intervals. In one report [13] such a regimen, based on repeat doses at intervals of 6 months, achieved a 1 year incidence of hypothyroidism as low as 2.2% but the cumulative rate in the survivors was 4–6% per year; in contrast to ablative therapists, they regarded this as a problem. The additional medical work involved here is reflected in the fact that 62% of their patients required between 2 and 5 additional doses. but 6% were still hyperthyroid after a mean follow-up of 3.6 years. In general these low rates are associated with persistent hyperthyroidism and the need for relatively costly continuing surveillance at specialist clinics.

Previous studies have been criticised on the grounds of patient selection, small numbers and short-term incomplete follow-up. In 1960–70 a prospective randomised trial took place in Sheffield using different radioiodine dose levels in patients with hyperthyroidism of Graves' disease. This report follows an earlier report on a smaller number of patients [14] and presents an analysis of the long-term clinical outcome

Address for correspondence: Ms S. J. Jones, Department of General Practice, Queen's Medical Centre, Nottingham NG7 2UH.

of this trial. It is linked to an economic appraisal of the treatment costs associated with different regimens incurred by both the health service and patients. The results obtained from the trial have been compared with the outcome of long-term follow-up of a separate group of patients treated using conventional but arbitrary methods for estimating the size of the treatment dose.

Methods and patients

Patients

Sheffield trial. A total of 660 patients were studied who fulfilled the usual criteria for the diagnosis of Graves' disease and hyperthyroidism. Selection for treatment with radioiodine in the Sheffield clinic was based on both social and clinical criteria including: aged over 30; completed family; sterilisation or effective use of contraception; and absence of compression symptoms from thyroid enlargement. The age distribution of the study group is shown in Table 1.

Patients selected for radioiodine therapy were randomly allocated to treatment with 3,500 rad (312) or 7,000 rad (323). A smaller number of patients (25) were treated and followed up after 14,000 rad.

Radioiodine was administered using the method of Blomfield *et al.* [15]. The size of the dose in millicuries (1 mCi = 37 MBq) to be administered to each patient to provide the intended rad dose to the thyroid, was calculated using the formula

$$\text{Expected rads/mCi} = \frac{820\times \text{48 hour tracer uptake (\%)}}{\text{Estimated gland weight (g)}}$$

The doses employed to deliver the desired number of rads to the thyroid are summarised in Table 1.

Patients were reviewed monthly until they became euthyroid; persistent hyperthyroidism was treated with antithyroid drugs if necessary; re-treatment with radioiodine was only carried out in patients with severe persistent hyperthyroidism. Twenty-six (8%) cases were re-treated in the 3,500 rad group and 13 (4%) in the 7,000 rad group. In patients who required it, antithyroid drug therapy was discontinued at 2 years to assess the response to radioiodine. Long-term follow-up in euthyroid patients was carried out at intervals of 6 months and losses and withdrawals from follow-up were documented in the patients' clinical records. The total period of follow-up ranges from 2 to 20 years (mean 8.7 years).

Scottish Automated Follow-up Register (SAFUR). SAFUR is a multi-centre, computer-based follow-up system which supports a general practice and specialist shared-care scheme for post-treatment thyroid patients [16, 17]. SAFUR patients were treated on the basis of a clinical assessment of thyroid enlargement (and in some cases the 48 hour thyroid uptake) and the selection of a dose of radioiodine from an arbitrary scale of low, intermediate and high doses.

In each of the five treatment centres the modal dose of radioiodine administered was 370 MBq. The treatment patterns and outcomes have been examined in a total of 3,920 radioiodine treated patients followed by SAFUR. Information available from the patients' computer-held follow-up records includes the number and size of radioiodine doses administered, the proportion of patients who required further doses for persistent hyperthyroidism and the cumulative proportion developing hypothyroidism after registration in the follow-up system. The distribution of total radioiodine administered is shown in Table 1. The average interval between radioiodine treatment and registration for follow-up in SAFUR was 3 years. In this interval, repeat doses for persistent hyperthyroidism were given and thyroxine replacement started for hypothyroidism. At the time of registration in SAFUR, 2,282 patients (58% of the total) were receiving full replacement therapy with thyroxine and 1,638 (42%) were euthyroid without replacement and provide the basis of estimates of late onset hypothyroidism. The mean follow-up period

Table 1. Ages of patients treated by three different dose regimens in Sheffield and SAFUR.

Treatment group		Age in year of treatment			Dose (megabecquerels)		
	n	Mean (SEM)	Median	Range	Mean (SEM)	Median	Range
Sheffield (rad dose)							
3,500	312	53.1 (0.5)	52	34–76	104 (33)	89	37–555
7,000	323	55.4 (0.5)	54	32–81	185 (4)	163	67–559
14,000	25	56.3 (1.9)	55	40–76	377 (19)	355	222–550
SAFUR (MBq dose)							
37–185	280	54.0 (0.6)	53	32–84	166 (2.1)	185	37–185
186–370	2,179	55.0 (0.2)	54	30–86	315 (1.2)	333	193–370
371–555	747	55.2 (0.4)	54	32–87	511 (1.9)	555	372–555
556–740	322	55.7 (0.6)	55	31–85	681 (3.3)	703	556–740
741+	372	53.3 (0.5)	52	31–88	1,199 (24.0)	1,073	770–3,885

in the group studied is 8 years; their age distribution is shown in Table 1.

Analysis of clinical outcome

The cumulative proportions with persistent hyperthyroidism and late onset hypothyroidism in the three Sheffield trial groups and late onset hypothyroidism in SAFUR were calculated using an actuarial life table method [18]. This is applicable to a follow-up study in which the patients have been observed for varying periods of time, withdrawals have occurred because of losses to follow-up, death, progress to alternative forms of treatment or limited follow-up during the period of study.

The outcomes of treatment, in terms of the cumulative proportions with persistent hyperthyroidism or late onset hypothyroidism, are presented as rounded point estimates with 95% confidence limits (95 CL). In the Sheffield trial the cumulative proportion who entered a remission after treatment was estimated using the whole group for a particular rad dose as the denominator (adjusted for withdrawals) and the first recorded date on which the patient was found to be euthyroid. For the cumulative proportion developing hypothyroidism, the denominator for both the Sheffield and SAFUR groups includes only those patients who had become euthyroid during any interval of the follow-up study.

Costs of medical treatment and follow-up

The treatment policies adopted in both Sheffield and SAFUR have been evaluated in terms of the medical work and costs associated with them. The areas of interest included initial radioiodine therapy, follow-up monitoring, reassessment and re-treatment.

The predicted outcome of treatment, in terms of persistent hyperthyroidism or hypothyroidism, was used to estimate the amount of medical work required in each of these areas for each treatment group. The general approach used in this economic appraisal and assumptions about the frequency of follow-up reviews have been described in a report on earlier follow-up studies using a computer-based follow-up system for thyroid disease [17]. Costs were estimated for medical work including outpatient department and general practice reviews [19,20], radioiodine treatment [21] and associated consultations and assessment services such as clinical chemistry [22], together with transport and patients' time for travel, waiting and consultation [23]. Annual clinical workloads were calculated for the total clinic population which would have accumulated after 10 years, assuming that 100 referrals took place in each of the preceding years. The resulting heterogeneous mixture of patients would thus reflect a typical cross-sectional clinic case load. Costs to both health service and patients were then calculated for this annual workload.

Results

The cumulative proportions of persistent hyperthyroidism in Sheffield and late onset hypothyroidism in both Sheffield and SAFUR are shown in Table 2 and Figs 1 and 2.

Sheffield trial: persistent hyperthyroidism and hypothyroidism

The clinical outcome of treatment with three dose levels of radioiodine is shown in Table 2 and Fig. 1. The low-dose regimen made little impact on persistent hyperthyroidism; 78% were still hyperthyroid at the end of the first year and 35% at the end of 5 years. The corresponding figures for 7,000 rad were 63% and 22%. The highest dose of radioiodine was more successful in eliminating hyperthyroidism, but all three regimens were associated with a residual group of patients (12–16%) who required continuing antithyroid drug therapy for hyperthyroidism at 10 years after treatment. The early and late proportions with hypothyroidism were lowest in the 3,500 rad group and showed the expected gradient across the three dose levels. However, in those who became euthyroid the differences in the life table predictions of hypothyroidism between the dose levels are small in clinical terms. They range from 14% to 25% at 5 years and from 28% to 39% at 10 years. Total 'morbidity', in terms of persistent hyperthyroidism and hypothyroidism, showed little variation between the three treatment groups (45–51%), but persistent hyperthyroidism as a proportion of this figure was higher with the lowest dose regimen.

Table 2. Sheffield: persistent hyperthyroidism and late onset hypothyroidism after radioiodine therapy at 1, 5 and 10 years after treatment.

Rad dose	Proportion (%) (95 CL) with persistent hyperthyroidism after treatment for			Proportion (%) (95 CL) with late onset hypothyroidism after treatment for			Persistent hyperthyroidism as % of total morbidity at 10 years
	1	5	10 years	1	5	10 years	
3,500	78 (72–83)	35 (29–40)	16 (11–21)	3 (1–5)	14 (10–19)	28 (21–35)	89
7,000	63 (56–70)	22 (17–26)	12 (8–16)	5 (3–8)	21 (16–26)	33 (27–39)	38
14,000	35 (7–61)	17 (2–33)	12 (0–25)	10 (0–23)	25 (6–44)	39 (16–62)	25

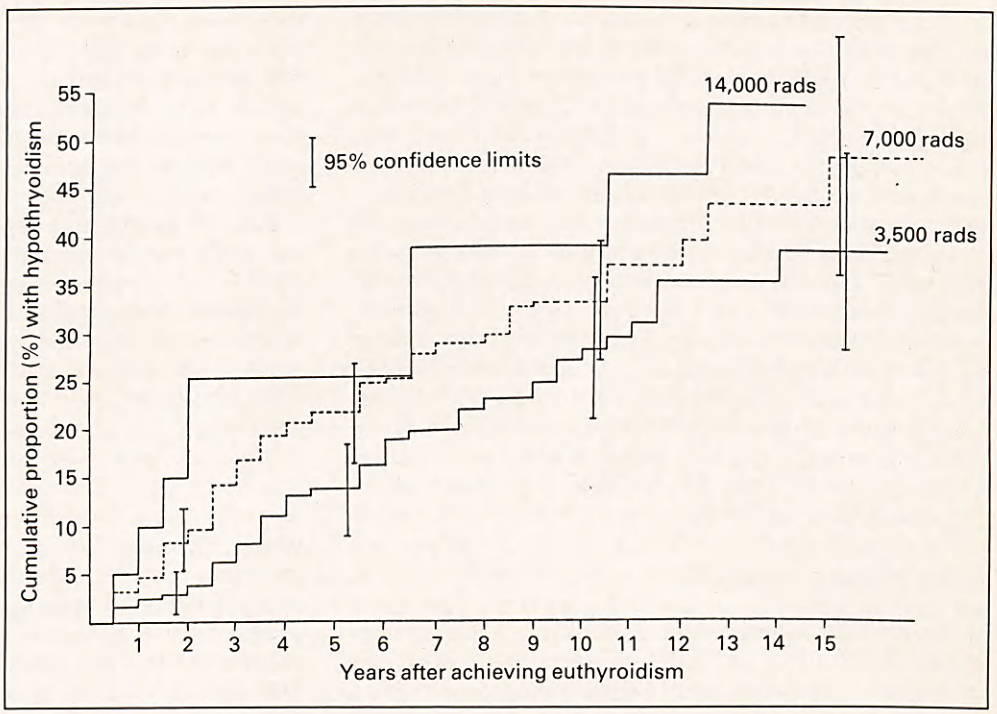
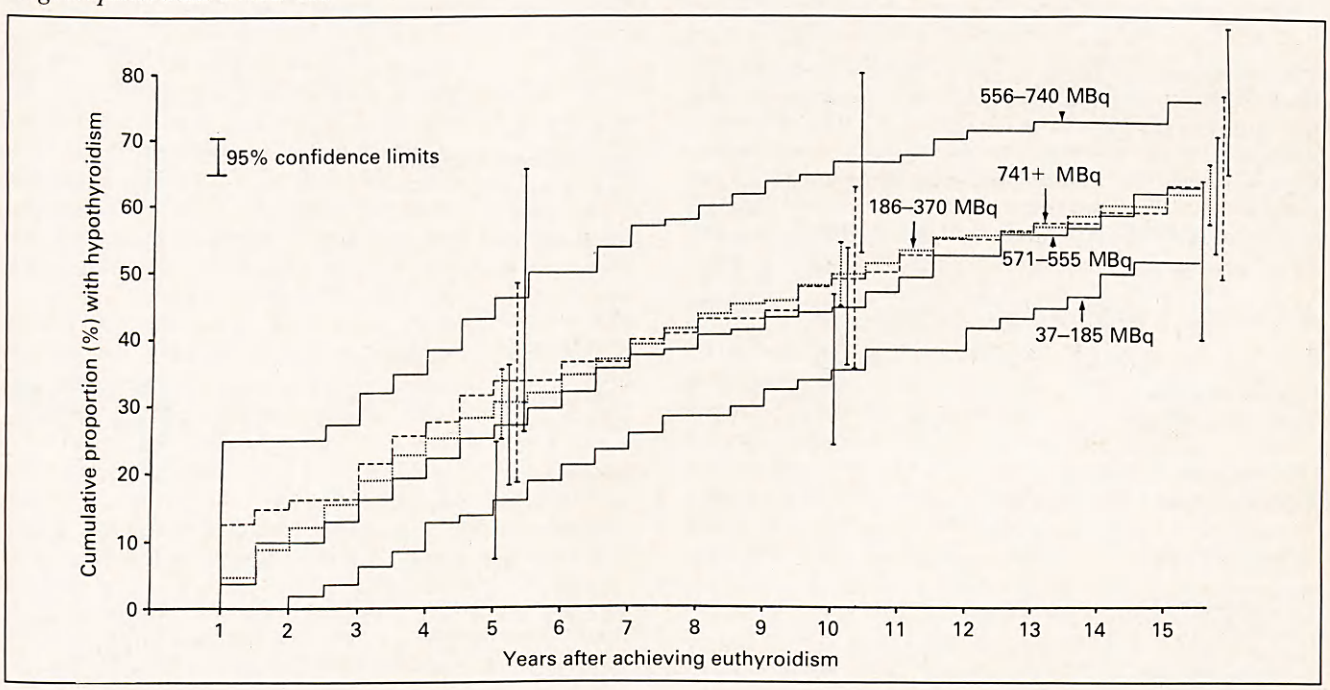


Fig. 1. *Predicted cumulative proportion with late onset hypothyroidism, after achieving a euthyroid state, following 3,500, 7,000 and 14,000 rad doses.*

SAFUR

In the five centres, out of a total of 3,920 patients, 469 (mean 19%, range 16–23%) required a second dose for persistent hyperthyroidism and 147 (mean 6%, range 4–10%) required a third dose. No cases of persistent or recurrent hyperthyroidism have been identified after registration in SAFUR over a period of 22 years. Repeat doses were required more often in the lowest dose group (33%) but there was little difference in re-treatment ratios between 186–370 MBq (23%) and 371–555 MBq (26%). The figure of 31% for the small group treated with 556–740 MBq probably reflects the difficulties of treating patients with large or nodular glands which are resistant to irradiation.

Fig. 2. *Predicted cumulative proportion with late onset hypothyroidism, after achieving a euthyroid state, following different megabecquerel doses in SAFUR.*



The cumulative proportion developing hypothyroidism was estimated in those who were euthyroid at the time of registration. The clinical outcome of treatment, based on an arbitrary scale of low, intermediate and high doses, shows a similar pattern to that observed in the Sheffield trial based on precision dosimetry. In the trial, lower rates of hypothyroidism were achieved at all dose levels but the differences between these groups and patients in SAFUR who received 186–555 MBq were relatively modest after 10 years. The cumulative proportions with hypothyroidism ranged from 25–30% in the lowest dose groups (3,500 rad and 37–185 MBq) through 30–40% (7,000 rad and 186–370 MBq) up to 40–50% in the 14,000 rad and 371–555 MBq groups. In SAFUR the 556–740 MBq group had considerably higher hypothyroid rates at 10 years (58%) than any of the other treatment regimens.

Medical workloads and costs

The workload associated with the four treatment regimens, in terms of patients' contacts with specialists and general practitioners (GP) per year, is shown in Table 3. It is based on a treatment service which has been running for 10 years with 100 referrals each year. It indicates the number of contacts and the reasons for them in both new referrals and returning patients who were initially treated in each of the preceding 10 years. The work represented in the table will be carried out in the eleventh year of the service.

The number of contacts for treatments with radioiodine in this year is higher for SAFUR patients because of the policy of routinely re-treating patients with persistent hyperthyroidism; the excess of 140 contacts for this service represents a mixture of patients receiving second, third or subsequent doses for persistent hyperthyroidism. However, the outpatient department contacts for persistent hyperthyroidism are lowest in SAFUR patients and tenfold higher in the lowest dose regimen in Sheffield. The need for medical work in the outpatient department (OPD) is greater by 130–170% in the intermediate and low dose Sheffield groups compared to the SAFUR group.

For the other component of care, provided by GPs, the workload for patients in SAFUR is at least 25% greater than with the regimens based on precision dosimetry. These gradients in workloads are reflected in the annual costs of providing services for the four treatment options after they have been established for 10 years (Table 4). SAFUR patients incur high costs in the early stages of treatment, since some require more expensive clinic time for re-treatment with radioiodine. In contrast, the Sheffield groups require more intensive follow-up for persistent hyperthyroidism which, for some, continues for many years. These high follow-up costs result in the overall higher costs, particularly for the 3,500 rad group. Patient costs are lower in the SAFUR group by 10–30% compared with the other treatment options. Although there are striking differences between the cost of the individual components of care, *overall* costs show relatively little variation between the four treatments.

Table 3. Annual workloads (numbers of visits to clinics) associated with 100 referrals per annum after 10 years, by original treatment regimen.

Type of contact (outpatient (OPD) or general practice (GP))	Sheffield treatment regimen			SAFUR regimen
	3,500 rad	7,000 rad	14,000 rad	
RAI treatment at OPD	400	400	400	540
OPD visit for persistent hyperthyroidism (every 6 months)	748	520	374	70
OPD visits for hypothyroidism	99	100	124	140
Total OPD visits	1,247	1,020	898	750
GP reviews (euthyroid/ hypothyroid)	501	561	571	711

Table 4. Annual costs (£) associated with 100 referrals per annum after 10 years.

Type of contact (outpatient (OPD) or general practice (GP))	Sheffield treatment regimen			SAFUR regimen
	3,500 rad	7,000 rad	14,000 rad	
RAI treatment at OPD				
NHS costs	17,920	17,920	17,920	24,192
Patient costs	2,580	2,580	2,580	3,483
OPD visits for persistent hyperthyroidism (every 6 months)				
NHS costs	12,566	8,736	6,283	1,176
Patient costs	4,825	3,354	2,412	452
OPD visits for hypothyroidism				
NHS costs	1,663	1,680	2,083	2,352
Patient costs	639	645	800	903
GP reviews				
NHS costs	4,604	5,156	5,248	6,534
Patient costs	997	1,116	1,136	1,415
Total NHS costs	36,753	33,492	31,534	34,254
Total patient costs	9,041	7,695	6,928	6,253
Total costs	45,794	41,187	38,462	40,507

Discussion

The data from the two studies presented here are based on relatively large numbers of patients selected for treatment on the basis of clinical criteria which are widely accepted. Allowing for the possibility of regional variations in disease outcomes, the results are likely to represent the outcome of radioiodine treatment and its costs in many centres in the United Kingdom for patients who receive similar doses. For patients who receive some form of prescriptive follow-up and surveillance (and this should include everyone) the results indicate the potential clinical benefits or disadvantages of modifying the dose of radioiodine and the amount and nature of the medical workload which would follow, together with the total costs incurred by both the health service and patients.

Low-dose radioiodine therapy leads to a high proportion of patients with persistent hyperthyroidism which resolves only slowly; in the trial this was highest in the 3,500 rad group. Even in the 14,000 rad group there was a residual proportion of 16% with persistence at 10 years; there was no indication that remissions were continuing to occur in this group, and as an indicator of the need for re-treatment this figure is very similar to the proportion who were re-treated in SAFUR in the intermediate dose levels of 371–555 MBq. Although very low doses are associated with higher levels of persistence, there appears to be a group of patients, approximately 15–25% of all those treated, who will be resistant to an initial dose of any size. This finding was consistent in five independent centres using SAFUR. True recurrences are rare and were not observed either in the Sheffield trial or in SAFUR patients who had become euthyroid.

The pattern of early and late hypothyroidism shows the expected relationship with dose levels in the trial. In comparison with the arbitrary scale related to thyroid size, precision dosimetry avoids hypothyroidism at the expense of persistent hyperthyroidism. Nevertheless, the lowest proportion with hypothyroidism at 10 years, in the 3,500 rad group, amounted to nearly one-fifth of those treated. The information generated by this trial and from the follow-up of SAFUR patients suggests that low-dose regimens, whether based on single or multiple treatments, are unlikely to avoid hypothyroidism in around 30% of the treated population at 10 years follow-up. The difference between precision dosimetry and prescribing by an arbitrary scale was relatively small at higher dose levels; there is no difference of any clinical significance in terms of the proportion with hypothyroidism. The results from the 3,500 rad group suggest that in lower dose regimens, without early re-treatment, the time elapsed before half the population achieves a remission is 31 months, while the corresponding period for 80% to remit is 105 months. In the intermediate dose range of 7,000 rad these intervals are reduced to 18 and 66 months respectively while, after treatment with 14,000 rad, 65% remitted within the first 6 months.

In considering the utility of different treatment plans for radioiodine treatment of hyperthyroidism, three factors should be considered: first, the quality of life and health experienced by patients and the risks associated with a particular regimen; second, the medical work required from both specialists and GPs to maintain adequate management; and third, the costs to the health service and patients. A salient feature of low-dose therapy, designed to avoid early hypothyroidism and dependency on replacement therapy, is that the majority of patients can expect to need antithyroid drugs to control hyperthyroidism for over 2 years. On the other hand, patients who become hypothyroid may proceed quickly to treatment with thyroxine replacement, and the majority can expect to remain euthyroid with only infrequent and minor adjustments to daily doses. The average incidence of inadequate replacement is about 1% per annum in patients who are properly informed about the need for continuous treatment [24]. After initial stabilisation, reassessment every 18–24 months would provide adequate monitoring of progress and identify patients who require further investigation and adjustment of thyroxine dosage.

There is no information on what patients would prefer if they were given the choice between continuing treatment with drugs for suppression of hyperthyroidism or higher doses of radioiodine and re-treatment to eliminate hyperthyroidism but with a high risk of hypothyroidism and the need for replacement. Their choice may reflect the cost and inconvenience of attending specialist clinics. We estimated that patient costs for OPD contact were three times higher than those for a GP contact. As well as follow-up for persistent hyperthyroidism being more costly per visit, patients will also need to make more frequent contact. Thus patients attending the OPD may incur annual costs which are some four times higher than those having GP follow-up. We have found that patient costs may amount to more than 20% of the total costs of treatment and follow-up after radioiodine therapy but they do not usually feature in a clinical appraisal of treatment choices for hyperthyroidism.

Medical costs of treatment are highest in the 3,500 rad group and patients' costs lowest in the SAFUR regimen. The overall costs of treatment show relatively little variation between 7,000 and 14,000 rad groups and SAFUR. The SAFUR population was treated as a whole group in the economic appraisal. There is some variation in the re-treatment ratios between different dose levels but they are relatively small and would not lead to substantially different conclusions if analysed separately. The modal dose in SAFUR is 370 MBq, so clinics using doses less than this would expect more medical work to be done in re-treating persistent hyperthyroidism and vice versa. This appraisal of costs indicates where savings may be made, for both the health service and patients, by modifying the initial treatment and the plans for further follow-up. However, the results suggest that the marginal costs to the service would be relatively less important than ensuring that management plans are the best possible for patients

from the point of view of convenience, comfort and expense. Additional studies on patients' subjective health and treatment preferences would be a useful addition to the evaluation of all treatments for hyperthyroidism.

In conclusion, this study indicates that very low total morbidity is unlikely to be achieved by any manipulation of radioiodine dosage. Very low dose regimens avoid hypothyroidism only at high cost in terms of long-term antithyroid drug therapy and inconvenience and expense to the health service and patients. Intermediate doses were more effective at eliminating hyperthyroidism, but the early relatively high levels of persistence are also associated with an appreciably high incidence of late onset hypothyroidism. High-dose regimens were associated with the lowest levels of persistence and the lowest overall costs to the health service and patients. High rates of hypothyroidism in these patients may be acceptable if the condition is detected and treated early; this can be assured by organised follow-up.

The optimal choice of treatment should be based on the quality of life for patients, medical work and costs, as well as the outcome of the radiobiological effects of radioiodine on the thyroid. The results of this survey indicate that larger doses of radioiodine, at least of the order of 370–555 MBq, are necessary to achieve early elimination of hyperthyroidism, to contain medical work and the costs associated with it.

Acknowledgements

We gratefully acknowledge the work of Mrs Helen Thomson in the SAFUR registry, the Scottish Health Service for support of SAFUR and the Scottish Home and Health Department (Chief Scientist office) for research funds. Mr K. J. Murray provided assistance with data analysis.

References

1. Hertz, S. and Roberts, A. (1942) Application of radioiodine in therapy of Graves' disease. *Journal of Clinical Investigation*, **21**, 624–33.
2. Chapman, E. M. and Evans, R. D. (1946) The treatment of hyperthyroidism with radioactive iodine. *Journal of the American Medical Association*, **131**, 86–91.
3. Beling, U. and Einhorn, J. (1961) Incidence of hypothyroidism and recurrences following ^{131}I treatment of hyperthyroidism. *Acta Radiologica*, **56**, 275–88.
4. Dunn, J. T. and Chapman, E. M. (1964) Rising incidence of hypothyroidism after radioactive-iodine therapy in thyrotoxicosis. *New England Journal of Medicine*, **271**, 1037–42.
5. Chapman, E. M. and Maloof, F. (1955) The use of radioactive iodine in the diagnosis and treatment of hyperthyroidism: ten years experience. *Medicine* (Baltimore), **34**, 261–321.
6. Blomfield, G. W., Eckert, H., Fisher, M. *et al.* (1959) Treatment of thyrotoxicosis with ^{131}I: a review of 500 cases. *British Medical Journal*, **1**, 63–74.
7. Philp, J. R., Harrison, M. T., Ridley, E. F. and Crooks, J (1968) Treatment of thyrotoxicosis with ionising radiation. *Lancet*, **ii**, 1307–10.
8. Glennon, J. A., Gordon, E. S. and Sawin, C. T. (1972) Hypothyroidism after low dose ^{131}I treatment of hyperthyroidism. *Annals of Internal Medicine*, **76**, 721–3.
9. McDougall, I. R. and Greig, W. R. (1976) ^{131}I therapy in Graves' disease: long-term results in 355 patients. *Annals of Internal Medicine*, **85**, 720–3.
10. Gimlette, T. M. D. and Hoschi, R. (1973) Treatment of thyrotoxicosis with iodine-125 in moderately low dosage. *Clinical Radiology*, **24**, 263–6.
11. Kendall-Taylor, P., Keir, M. J. and Ross, W. M. (1984) Ablative radioiodine therapy for hyperthyroidism: a long-term follow-up study. *British Medical Journal*, **289**, 361–3.
12. Young, R. E. and Hedley, A. J. (1984) Ablative radioiodine therapy for hypothyroidism: a long-term follow-up study (letter). *British Medical Journal*, **289**, 829.
13. Hoskin, P. J., McCready, V. R., Harmer, C. L. *et al.* (1985) Low dose radioiodine given six monthly in Graves' disease. *Journal of the Royal Society of Medicine*, **78**, 893–7.
14. Smith, R. N. and Wilson, G. M. (1967) Clinical trial of different doses of ^{131}I in treatment of thyrotoxicosis. *British Medical Journal*, **1**, 129–32.
15. Blomfield, G. W., Jones, J. C., Macgregor, A. G. *et al.* (1955) Treatment of thyrotoxicosis with radioactive iodine: review of 140 cases. *British Medical Journal*, **2**, 1223–9.
16. Hedley, A. J., Scott, A. M. and Debenham, G. (1969) A computer assisted follow-up register. *Methods of Information in Medicine*, **8**, 67–77.
17. Jones, S. J., Hedley, A. J., Curtis, B. *et al.* (1982) Do we need thyroid follow-up registers? A cost-effective study. *Lancet*, **i**, 1229–32.
18. Armitage, P. and Berry, G. (1987) *Statistical methods in medical research*, 2nd edn. Oxford: Blackwell Scientific Publications.
19. Department of Health and Social Security (1987) *Health services costing returns.* London: HMSO.
20. Review body on doctors' and dentists' remuneration (1987) Seventeenth report. London: HMSO.
21. Department of medical physics (1987) University Hospital, Nottingham.
22. Department of biochemistry (1987) Glasgow Royal Infirmary, Glasgow.
23. Central Statistical Office (1987) *Annual abstract of statistics.* London: HMSO.
24. Scottish Automated Follow-up Register Group (1980) Thyroxine replacement therapy: prescribing patterns and problems in 2710 patients. *British Medical Journal*, **281**, 969–71.