

# Intermediate and Long-Term Side Effects of High-Dose Radioiodine Therapy for Thyroid Carcinoma

Christof Alexander, Jochen B. Bader, Andrea Schaefer, Carsten Finke and Carl-Martin Kirsch  
*Department of Nuclear Medicine, Saarland University Medical Center, Homburg/Saar, Germany*

The present investigation is an evaluation of intermediate and long-term side effects in patients after high-dose radioiodine treatment due to differentiated thyroid carcinoma. **Methods:** A total of 203 patients were interviewed using a standardized questionnaire. **Results:** After radioiodine treatment, 76.8% of the patients reported intermediate (from discharge up to 3 mo) or long-term (more than 3 mo after treatment) complaints, and 61.1% reported long-term side effects. Nonstochastic side effects included sialoadenitis, which occurred in 33.0% of cases, and 27.1% of patients suffered from a transient loss of taste or smell. More than 1 yr after the last radioiodine application, 42.9% of patients suffered from reduced salivary gland function. Complete xerostomia occurred in 4.4% of patients. Hematological abnormalities were found in 9 patients. In 28.1% of patients a transient episode of alopecia was reported. In 22.7% of patients chronic or recurrent conjunctivitis was reported, and 4 patients underwent dacryocystorhinostomy; 13.8% of patients suffered from an increased frequency of influenza, but 3.4% reported a reduced occurrence of such infections. For sialoadenitis, the loss of taste/smell and dry mouth, the dependence on accumulated activity was significant. **Conclusion:** Severe long-term side effects are rare after high-dose radioiodine treatment. Moderate side effects are common. The side effects are commonly the result of radiation damage to the salivary glands. The frequency of such complaints advocates regular protection of the salivary glands.

**Key Words:** radioiodine therapy; differentiated thyroid carcinoma; long-term nonstochastic side effects

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Radioiodine treatment for differentiated thyroid carcinoma has been around 52 yr (1). During this long period of continuous gain in experience, the favorable therapeutic effects for well-differentiated thyroid carcinoma have become clear.

Other relevant information was accumulated concerning stochastic side effects of this regimen such as the rates of miscarriage and prematurity, and this major congenital anomaly is not significantly different from the general population (2-5). The post-therapeutic risk of other neoplasms is slightly increased for breast and bladder cancer (6,7), and the incidence of radiation leukemogenesis is low (8-12).

Nonstochastic immediate side effects during hospitalization, such as radiation thyroiditis, nausea, vomiting, epigastralgia and sialadenitis are common (13). Serious acute complications are extremely rare (2,7,14-16); however, little information is available on nonstochastic intermediate and long-term side effects. The present investigation was a retrospective evaluation of intermediate and long-term complaints and side effects of patients after high-dose radioiodine treatment.

## MATERIALS AND METHODS

The therapy regimen for this study was as follows: ablation of thyroid remnants was performed 4-6 wk after total thyroidectomy

by a standard activity of 3.7-7.4 GBq (100-200 mCi) <sup>131</sup>I. Repeated treatments were done in cases of persisting thyroid remnants/functioning metastases by standard activities of 7.4-9.3 GBq (200-250 mCi) every 3 mo for 1 yr. If further treatments were necessary, these were performed once or twice a year depending on bone marrow recovery.

To avoid damage to the salivary glands, all patients were advised to increase their fluid intake, chew gum and suck on sour candies to promote discharge of radioiodine from the glands. In addition, pilocarpine was given orally in patients who tolerated this regimen.

In the course of follow-up of differentiated thyroid carcinoma from July 1996 to August 1997, 203 patients were interviewed by an experienced nuclear medicine physician using a standardized questionnaire. The following questions were selected according to well-known side effects and to complaints that were reported more frequently in the course of follow-up:

1. Did you suffer from pain or swelling in the parotid/submandibular region after radioiodine treatment? If yes, which regions were involved?
2. Did your mouth become drier? Did you notice an increased production of viscous mucus or a morning expectoration since therapy?
3. Is your mouth completely dry so that you are unable to eat without drinking?
4. Did you lose taste or smell after radioiodine therapy?
5. Do you suffer often or continuously from red eyes, conjunctivitis or increased lacrimation?
6. Did you notice an increased frequency of colds, influenza or angina since your radioiodine treatment?
7. Have you had increased loss of hair after therapy?
8. Have you persistent vocal cord paralysis? If yes, on which side?
9. Did you have a tracheostoma after thyroidectomy?
10. Have you a regular medication of calcium or vitamin D because of a postoperative hypoparathyroidism?

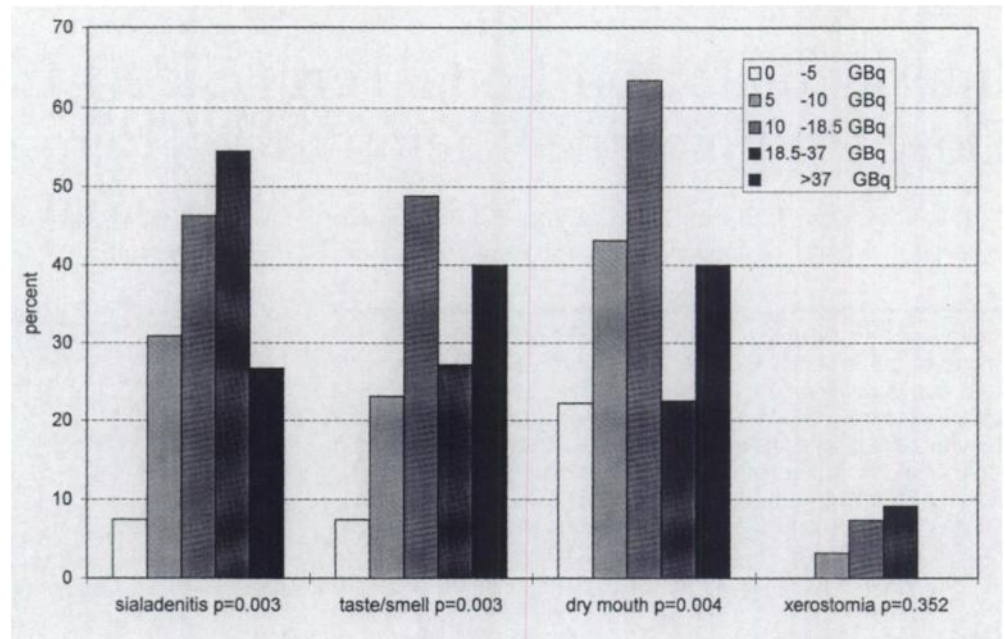
The questionnaire included complaints that were reported regularly by follow-up patients, no matter if the cause was surgery or radioiodine treatment or was unclear. They were divided into intermediate (from discharge up to 3 mo) and long-term (more than 3 mo after treatment) effects. Additionally, the patients were asked to volunteer complaints outside those asked as standard questions. The criterion for the distinction between "dry mouth" and complete "xerostomia" was that in the latter case food could not be swallowed without additional simultaneous drinking.

The mean age of the group at follow-up was  $51 \pm 14$  yr (mean  $\pm$  s.d.). Fourteen patients with additional percutaneous radiotherapy of head and neck were excluded. The period between the last radioiodine treatment and the interview was longer than 1 yr. It ranged from 1 to 21 yr, and the mean time interval was 5 yr. Additionally, a complete blood count was performed in every patient to look for hematological abnormalities. Spermatogenesis and ovarian function were not evaluated.

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For correspondence or reprints contact: Christof Alexander, MD, Department of Nuclear Medicine, Saarland University Medical Center, D-66421 Homburg/Saar, Germany.

**FIGURE 1.** Nonstochastic, dose-dependent, intermediate (sialoadenitis, loss of taste/smell) and long-term (dry mouth, xerostomia) side effects of high dosage radioiodine therapy for groups of increasing cumulative activities; p values are from Pearson chi-square test.



Absolute and relative rates of side effects were counted for all patients and for groups of different cumulative activities. Total activity administered ranged between 4.4 and 69.0 GBq (0.1-1.9 Ci). Five groups were formed: (a) cumulated activity was 0 to < 5 GBq (0-<135 mCi) for Group I (n = 38); (b) 5 to < 10 GBq (135-<270 mCi) for Group II (n = 71); (c) 10 to < 18.5 GBq (270-<500 mCi) for Group III (n = 53); (d) 18.5 - <37 GBq (0.5-<1 Ci) for Group IV (n = 24); and (e)  $\geq 37$  GBq ( $\geq 1$  Ci) for Group V (n = 17). The rate of postoperative complications (vocal cord paralysis, hypoparathyroidism) was also documented. An additional comparison was performed for patients with and without pilocarpine medication during radioiodine treatment.

For statistical analysis,  $2 \times 2$  and  $5 \times 2$  contingency tables and the chi-squared test were used. The significance values were calculated using Pearson's correlation coefficient, a significant difference between groups of different cumulated activities was evident for p values < 0.05. An additional Mantel-Haenszel test for linear association was performed.

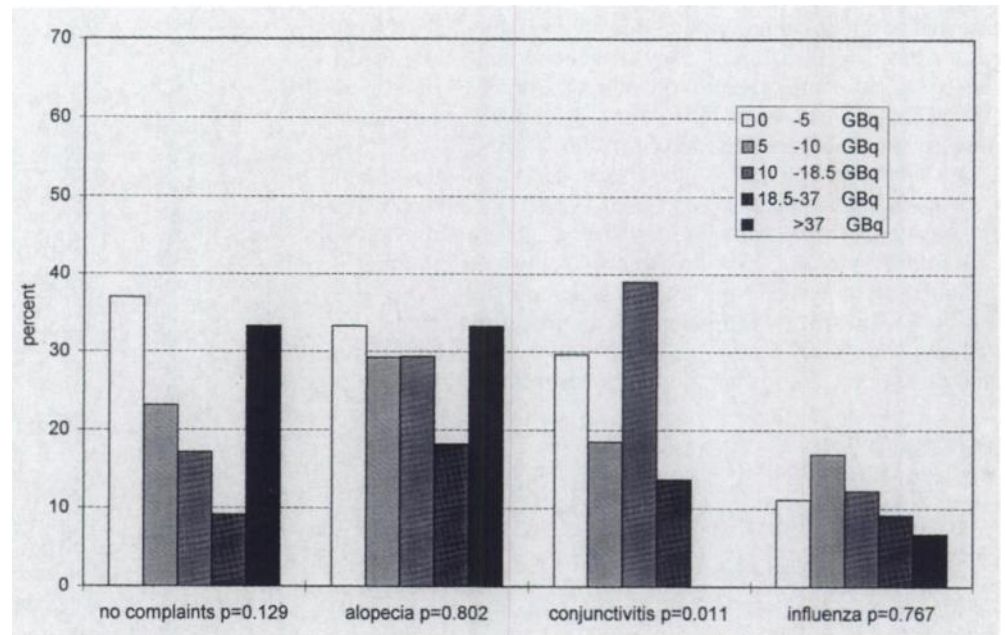
**RESULTS**

The rates of the nonstochastic, intermediate and long-term side effects and of the other, nondose-dependent complaints for groups of increasing cumulative activities are documented in Figures 1 and 2. Persistent paralysis of the vocal cords was seen as a postoperative complication in 18.2% (37/203) of patients, and in 2.0% (4/203) of cases, both sides were involved. The rate of postoperative hypoparathyroidism was 9.4% (19/203) and of persistent tracheostoma 1.0% (2/203).

After radioiodine treatment, 76.8% of patients (156/203) reported intermediate or long-term complaints, of which 61.1% (124/203) showed long-term side effects more than 1 yr after the last  $^{131}\text{I}$  application.

The intermediate complaints were documented as follows: sialoadenitis occurred in 33.0% of cases (67/203). In 80.6%, (54/67) the parotid gland (unilateral: 14; bilateral: 40); and, in 46.3% (31/67), the submandibular gland (unilateral: 8, bilateral: 23) was affected. The frequency of sialoadenitis showed a dose dependence (p = 0.009) and a linear association to cumulative

**FIGURE 2.** Complaints after radioiodine therapy without dose dependence with significance values for groups of increasing cumulative activities.



activity ( $p = 0.004$ ). Twenty-seven percent (55/203) suffered from a transient, dose-dependent ( $p = 0.013$ ), linearly associated ( $p = 0.002$ ) loss of taste or smell. Another 28.1% (57/203) of patients reported a transient episode of alopecia. Loss of taste/smell and alopecia mostly occurred one to several weeks after discharge and lasted for 1 to 12 wk before normalization. In 13 patients, moderate alopecia persisted for more than 1 yr; this side effect was not dependent on administered  $^{131}\text{I}$  activity ( $p = 0.685$ ).

The following long-term complaints persisted during the intermediate period and were still present more than 1 yr after the last radioiodine application: 42.9% of patients (87/203) suffered from reduced salivary gland function that resulted in a dry mouth, increased production of viscous mucus or morning expectoration. Complete xerostomia occurred in 9 patients (4.4%). In 1 female patient, xerostomia resolved 7 yr after the last radioiodine treatment. A coincidence of dry mouth/xerostomia and post-therapeutic sialoadenitis occurred in 43 patients, a rate of 44.9% (43/96). Thus, more than half the cases of reduced salivary gland function did not arise from clinically evident sialoadenitis. For dry mouth, a dependence on cumulated activity was significant ( $p = 0.001$ ); there was no linear association to cumulative activity ( $p = 0.141$ ). The few cases of xerostomia gave no positive correlation ( $p = 0.360$ ).

In 46 cases, chronic or recurrent conjunctivitis was reported (22.7%), and 4 patients underwent dacryocystorhinostomy. Twenty-eight patients suffered from an increased frequency of influenza (13.8%), but another 7 patients (3.4%) reported a reduced occurrence of such infections. Both complaints were not dose-dependent ( $p = 0.233$  and  $p = 0.880$ ). For all evaluated complaints, there was no statistically significant difference between the patients who received pilocarpine during radioiodine therapy and those who did not.

Hematological abnormalities were found in 9 cases. These showed a moderate decrease of leukocytes in a complete blood count. The values ranged from 3,200–4,200/ $\mu\text{l}$  (normal range: 4,300–10,000/ $\mu\text{l}$ ). Thrombopenia, aplastic anaemia and signs of leukemia were not found.

## DISCUSSION

After total thyroidectomy, due to thyroid carcinoma, the rate of vocal cord paralysis ranges between 2.5% and 12.8%, that of hypoparathyroidism between 4.0 and 9.2% (7,17). Thus, our values of 17.1 and 10.0% are quite high. They are partly due to the results of multiple hospitals and medical centers in the surrounding areas; the majority of the patients did not undergo surgery at the Saarland University Medical Center. Often, when the diagnosis of cancer was made unexpectedly after a subtotal thyroidectomy because of the diagnosis of goiter, only second-line total thyroidectomy was performed in a major medical center. The results underline the necessity of adequate treatment of suspect cases in a medical center experienced in surgery of the thyroid.

Van Nostrand et al. (18) reported intermediate side effects in 10 of 15 patients and persistent effects in only 1 patient. These results are hardly comparable to ours because only single-dose applications were evaluated, and the total number of patients was low. Sialoadenitis is the most frequent intermediate side effect of high-dose radioiodine treatment (19–24). The documented frequencies vary from 10% to 60%, which is comparable to our result of 33.0% (10,18,22,23). Albrecht et al. (22) found an involvement of the parotid gland in 59% (30/51) and of the submandibular gland in 16% (8/51) of cases. Bilateral parotitis was more frequent (25/51) than unilateral (5/51). These results are comparable with our evaluation where, using a larger

patient group, the higher frequency of parotitis and the predominance of bilateral involvement is confirmed. The increased sensitivity of the parotid gland is an effect of its large proportion of serous tissue (ductal cells), which absorbs iodine to a higher concentration than the mucous tissue of the submandibular glands (22,24).

Albrecht et al. (22) documented a positive correlation of cumulative activity and the rate of sialoadenitis. The present results confirm this phenomenon. Furthermore, he reported a transient loss of taste in 58% (30/51) of patients. This dependence on administered activity was as follows: 0–11.1 GBq: 56%, 18.5–37 GBq: 53%, more than 37 GBq: 78% (22). The present evaluation gave a lower incidence of 27.1%, which includes a loss of smell in several cases. It also demonstrates a significant correlation of such complaints and accumulated activity.

In the literature only alopecia over functioning metastasis is mentioned (18). In our opinion, radiation exposure to hair follicles, which might be in the range of whole-body dose, is far from the dose that causes a loss of hair. So this transient, non-dose-dependent phenomenon cannot be a direct effect of radioiodine treatment. It is probably a result of thyroid hormone status disturbances that occur during the treatment of differentiated thyroid cancer. Patients go from euthyroidism over postoperative hypothyroidism to an iatrogenic hyperthyroxinaemia with suppressed thyrotropin levels caused by high-dose thyroid hormone replacement. Alopecia is a common symptom occurring in approximately one third of patients with hyperthyroidism. The percentage in our collective is of the same order, so the causes might be similar. Female patients, in particular, should be informed about this frequent cosmetic problem, to avoid unnecessary worry after discharge.

When other groups found that late complications after radioiodine treatment of thyroid carcinoma are uncommon, they confined themselves to severe nonstochastic effects: aplastic anaemia 0.0%–1.2%, lung damage 0.0%–0.4%, infertility 0.4%–12%, transient ovarian failure 25%, persistent oligospermia 0.4% (2,4,7,10,14,16,23,24). Brown et al. (2) rarely observed long-term xerostomia in a group of 235 patients. This correlates to our result of merely 4.4%. Leeper et al. (15) found the dry mouth to be a common complaint in a group of 46 patients. Albrecht et al. (22) reported a frequency of 22% (11/51). The present evaluation shows a percentage of 42%, which emphasizes these results. Albrecht et al. (22) reported a rate of dry mouth increasing with cumulated activity, which reached a maximum of 55% for patients with more than 37 GBq  $^{131}\text{I}$ . This trend for dry mouth and xerostomia is confirmed.

Measurements of function by salivary gland scintigraphy gave significant, dose-dependent reduction of flow rate, 10-min uptake and excretion in up to 73% of patients (23,24). Our data for dry mouth and xerostomia confirm these results.

Malpani et al. (24) found no significant difference in reduced salivary gland function between symptomatic and asymptomatic patients. The result corresponds with our finding that only 45% of patients with dry mouth reported post-therapeutic complaints of sialoadenitis.

The frequency of such complaints advocates a regular prevention of salivary gland damage and the development of more effective precautions. An interesting approach is the use of the cisplatin antidote and radioprotector amifostin (S-2-[(3-aminopropyl) amino] ethyl dihydrogenmonothiophosphate; Ethylol; Essex Pharma, München, Germany) before iodine application (25). This method appeared to be efficient, but it is quite expensive.

An increased frequency of influenza data is needed in the literature. The moderate value of 14% is not significant and is partially neutralized by those 3% patients who reported a reduced rate of colds. This phenomenon is not related to radioiodine dose.

The description of chronic and recurrent conjunctivitis is novel, it shows no significant dose dependence. The percentage of 23% is relevant, and the reported number of dacryocystorhinostomies underlines the severity of this problem. Thus, patient information before radioiodine application should include this long-term hazard.

One article reported gastrointestinal (GI) complaints in all patients who underwent multiple radioiodine treatments, and a dose dependence was not given (26). Another author found no intermediate or long-term GI complaints in 15 patients (18). No spontaneous report of such problems occurred over the years in our follow-up, so that a question referring to this was not included in the questionnaire. In our opinion, GI complaints are not relevant after the immediate phase.

Pilocarpin is an alkaloid with parasympathomimetic pharmaceutical effects. It is an excellent sialogogum that stimulates salivation up to 500 ml within several hours. As  $^{131}\text{I}$  is concentrated and excreted by the salivary glands, this medication was given to promote the discharge of iodine from the glands and to reduce the absorbed dose by a reduction of the effective half-time. A nonsignificant trend of reduced side effects was seen in the pilocarpine group, but finally the results could not demonstrate the expected protective effect.

As a complete blood count was performed more than 1 yr after the last application of  $^{131}\text{I}$ , the low rate of moderate leukopenia in 4.4% of cases is the expression of excellent recovery of the bone marrow. The documented slight leukopenia did not even reach WHO-Grade II hematotoxic reaction (leukocyte counts lower than  $3,000/\mu\text{l}$ ). High-dose therapy causes hematotoxic reactions in the intermediate phase up to WHO Grade III in 60%–90% of patients (16,18). But, long-term effects like aplastic anaemia or leukemia occur in less than 2% (2,8,12,16,17,19,24,26,27). Persistent leukopenia was reported in 10%–11% of cases (12). Our results might be explained by the lower proportion of patients with high cumulated activities over 18.5 GBq (0.5 Ci). The number of patients in these groups allows no statistically relevant determination of hematological abnormalities.

## CONCLUSION

These results demonstrate that severe long-term nonstochastic side effects are rare after high-dose radioiodine treatment of differentiated thyroid carcinoma. Moderate side effects are more common than mentioned in literature. Mostly they are the result of radiation damage to the salivary glands. An additional oral application of pilocarpine during radioiodine treatment cannot prevent salivary gland damage. The description of transient alopecia and chronic conjunctivitis after treatment of thyroid carcinoma is novel. No connection with radioiodine therapy could be proven. Nevertheless, in our opinion, it should be included in patient information before therapy to avoid unfounded worries after radioiodine treatment.

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